FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE PSYCHOPHARMACOLOGIC DRUGS AND DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEES

Thursday, October 16, 2014

8:00 a.m. to 4:00 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

Silver Spring, Maryland

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

Call to Order

Introduction of Committee

DR. PARKER: Good morning. I think it's 8:00. I am Ruth Parker, and I am the acting chair today of this group. And I'd like to welcome everyone. I'd also like to remind everyone to please silence your cell phones, smartphones, other devices if you have not already done so. And I'd like to identify the FDA press contact, Jenny Haliski. Thank you, Jenny, for waving at us.

I'd like to now go around the table and let everyone introduce themselves into the microphone if you don't mind. And we'll start with you, Dr. Michelson. Thank you.

DR. MICHELSON: Hi. I'm David Michelson from Merck. I'm the industry rep.

DR. SAXON: Andrew Saxon. I'm an addiction psychiatrist at the VA and the University of Washington in Seattle.

DR. MARDER: Steve Marder. I'm from UCLA and the VA Greater Los Angeles. And I'm a

psychiatrist.

DR. EMERSON: Scott Emerson, professor of biostatistics at University of Washington, Seattle.

DR. AUGUSTSON: Eric Augustson, program director, National Cancer Institute, tobacco control research branch.

DR. MORRATO: Elaine Morrato. I'm an epidemiologist in health services research in the Department of Health Systems, Management, and Policy at the Colorado School of Public Health.

DR. MALARCHER: I am Ann Malarcher. I'm a senior scientist, focusing on cessation, of the Office of Director, Office on Smoking and Health at CDC.

DR. BUDNITZ: I am Dan Budnitz from the Division of Healthcare Quality Promotion and Medication Safety program at CDC.

MR. BYRD: Christopher Byrd, patient representative from Orlando, Florida.

DR. PERRONE: I'm Jeanmarie Perrone. I'm professor of emergency medicine and medical toxicology from the University of Pennsylvania.

DR. GERHARD: Tobias Gerhard, pharmacoepidemiologist from the Rutgers Ernest Mario School of Pharmacy.

DR. ERSTAD: Brian Erstad, professor and head, University of Arizona College of Pharmacy.

DR. PARKER: Ruth Parker, professor of medicine, pediatrics, and public health, Emory University.

MS. BHATT: Good morning. I'm Kalyani Bhatt. I'm with the Division Advisory Committee Consultants Management.

DR. PICKAR: I'm David Pickar, associate adjunct professor of psychiatry at Johns Hopkins and Uniformed Services, former branch chief, intramural NIMH.

DR. BATTISTI: I'm John Battisti, specialty in neuropharmacology with Inventive Therapeutics Institute and associate professor.

DR. GRIEGER: Tom Grieger, psychiatrist with the Maryland Department of Health and Mental Hygiene.

DR. ROUMIE: Christianne Roumie, internal

medicine, pediatrics, Vanderbilt University and staff physician at the National VA.

DR. RIMAL: I'm Reggie Rimal. I'm professor in the School of Public Health, George Washington University.

DR. CHEN: Natasha Chen. I'm an epidemiologist from the Division of Epidemiology, Center for Drug Evaluation and Research, FDA.

DR. STAFFA: Judy Staffa, director, Division of Epidemiology, Center for Drugs at FDA.

DR. IYASU: Yeah. My name is Solomon Iyasu. I am the director of the office of pharmacovigilance and epidemiology at the Centers for Drugs.

DR. BULL: Bob Bull, deputy director, Office of Surveillance and Epidemiology, Center for Drugs.

DR. WINCHELL: Celia Winchell. I'm the medical team leader for addiction products in the Division of Anesthesia, Analgesia, and Addiction Products.

DR. RACOOSIN: Judy Racoosin. I'm the deputy director for safety in the Division of

Anesthesia, Analgesia, and Addiction Products.

DR. PARKS: Good morning. I'm Mary Parks, deputy director, Office of Drug Evaluation II.

DR. JENKINS: Good morning. I am John Jenkins. I'm the director of the Office of New Drugs in CDER.

DR. PARKER: Ms. McCarthy, if you would, introduce yourself as well.

MS. MCCARTHY: Elizabeth McCarthy. I'm a psychotherapist, Royal Oak, Michigan.

DR. PARKER: Thank you all very much.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these topics, and those individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now, I will pass it to my colleague, Kalyani Bhatt, who will read the conflict of interest statement.

Conflict of Interest Statement

MS. BHATT: Good morning. The Food and Drug Administration is convening today's joint meeting of the Psychopharmacological Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee under the authority of the

Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C., Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with the federal ethics and conflict of interest laws. Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees or regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or

her potential financial conflict of interest.

Related to the discussion of today's meeting, members and temporary members of these committees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of the safety data from observational studies and the meta-analysis of randomized controlled clinical trials that have been conducted since the original signal of serious, neuropsychiatric adverse events with Chantix, varenicline tartrate tablets, NDA 21928, Pfizer, Incorporated, emerged.

The committee will also discuss whether any actions needs to be taken with regards to how the risk is described in product labeling.

This is a particular matters meeting, during which specific matters related to Pfizer's NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. David Michelson is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Michelson's role at this meeting is to represent industry in general and not any particular company. Dr. Michelson is employed by Merck and Company.

We would like to remind members and temporary members that if the discussions involve

any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships they may have with the firm at issue. Thank you.

DR. PARKER: One remark to everyone. It's a little pronunciation. It's varenicline. I did confirm that. I had to ask a few times, but I've got the final word on it. So we can all say that and try to remember it, varenicline, not varenicline [clyne]. And it's Chantix with a C-H, not with an S.

So if you'd like to practice, we can, but I just wanted to get the record straight on that. It's varenicline and it's Chantix. But it's okay if we struggle with that, but that is the clarity for the record.

So we'll now proceed with Dr. Racoosin with introductory remarks. Thank you.

FDA Introductory Remarks and Regulatory History

Judith Racoosin

DR. RACOOSIN: Good morning, Dr. Parker, members of the Psychopharmacologic Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee, invited guests. Thank you for your participation in this important meeting.

We're here today to discuss a labeling supplement submitted by Pfizer in April of this year. In the cover letter for the submission, Pfizer stated the following:

"Since 2009, more reliable data on the neuropsychiatric safety of Chantix have become available, including meta-analyses of placebo-controlled clinical trials and data from observational studies comparing varenicline to other smoking cessation pharmacotherapies. As presented in this submission, these data do not support an association between treatment with Chantix and serious neuropsychiatric events."

In support of this assertion, Pfizer submitted the meta-analyses of randomized

controlled trials and their review of the observational studies mentioned in the cover letter.

This slide lists Pfizer's proposed labeling changes submitted in the labeling supplement. I have highlighted in red the changes we'll be focusing on today, specifically the removal of the boxed warning on serious neuropsychiatric events.

Over the past several months, the FDA team reviewed the data from the randomized controlled trial meta-analyses and observational studies and concluded that some of the information could be added to varenicline labeling in the warning about serious neuropsychiatric events, so that prescribers would have a full picture of what meta-analysis and observational studies have been conducted to enhance the understanding of varenicline-associated serious neuropsychiatric adverse events.

So why did FDA convene this advisory committee meeting? First, there is limited precedent for determining whether or when to remove

a boxed warning. And FDA believes that there is some additional data that we need before making such a decision.

Pfizer is coming close to completing a randomized controlled trial, required by FDA, that is designed to measure the incidence of serious neuropsychiatric adverse events with varenicline compared to other smoking cessation products and placebo. Pfizer anticipates submitting the final study report about one year from now.

FDA believes that the findings of this randomized controlled trial are essential to better understanding the association between varenicline and serious neuropsychiatric adverse events and that we shouldn't make a decision about the boxed warning until we have that data in hand.

However, because Pfizer believes the collection of observational and meta-analytic data are alone sufficient to support removal of the boxed warning, we're bringing this issue to the committee for discussion.

FDA fully appreciates that smoking cessation

is an important public health goal and that varenicline has been demonstrated in clinical trials to be an effective aid to smoking cessation. You will hear more about the regulatory rationale for the use of a boxed warning later this morning. In the case of varenicline, the boxed warning was placed because neuropsychiatric adverse events are a serious adverse event that can prevented or reduced in frequency or severity by appropriate use of the drug.

FDA believes that the determination of whether the boxed warning should be removed hinges on the scientific evidence available to assess the association between varenicline exposure and serious neuropsychiatric adverse events, not on the efficacy of the drug.

Next, I will summarize the regulatory history of the safety issue. It's important to remember that when a new safety issue emerges in the postmarketing period, that the understanding of the event evolves over a period of time as cases are reported to the drug manufacturer and to the

FDA. With accumulating information, FDA is better able to make an assessment about relatedness to drug exposure.

The European Medicines Agency first alerted FDA to the concern about suicidality with varenicline in May of 2007, about a year after FDA approval. Through the remainder of 2007 and into 2008, FDA reviewed adverse event reports submitted to FDA's adverse event reporting system as well as submissions from Pfizer, describing case reports that they had received.

As FDA's evaluation of the cases progressed and the level of concern regarding the association increased, the placement of labeling language about the association became more prominent, moving from adverse reactions to warnings and precautions, and culminating with the addition of a boxed warning in July of 2009.

With the passage of the FDA Amendments Act in September of 2007, FDA was granted additional postmarket safety authorities. Two of these were implemented for varenicline in May of 2008. First,

a risk evaluation and mitigation strategy, or REMS, was required, including a medication guide, or MedGuide, with patient-friendly language describing the risk of neuropsychiatric adverse events with varenicline.

We also implemented a postmarketing requirement that stated that Pfizer needed to conduct a postmarketing clinical study or trial of Chantix to assess the known serious risk of neuropsychiatric symptoms, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions.

This slide shows the number of unique patients receiving dispensed prescriptions for smoking cessation products through U.S. outpatient retail pharmacies from 2006 to 2013. The IMS Health Total Patient Tracker was used to obtain the nationally-estimated number of patients receiving dispensed prescriptions for Chantix, Zyban, generic and brand, NICOTROL inhaler, and NICOTROL nasal spray through U.S. outpatient retail pharmacies for the years 2006 through 2013. Chantix was approved

in mid-2006.

Note that this slide only includes products labeled for smoking cessation, so it does not include products that may be used off-label, such as Wellbutrin SR or XL or generic bupropion products. This slide also shows the timing of the implementation of the labeling changes and postmarket safety authorities that I have described.

The decline of varenicline prescriptions from a peak of about 3.9 million prescriptions in 2007 followed the placement of the warning statement and implementation of the REMS. As is shown on the slide, the decline in sales preceded the placement of the boxed warning in July of 2009.

All risk evaluation and mitigation strategies, or REMS, are required to have assessments performed at specific intervals. Results from the first two REMS assessments for varenicline are available.

The assessment plan included an evaluation of patients' understanding of the serious risks of

Chantix via survey. The results were similar for the 18-month and 3-year assessments. About 70 to 80 percent of patients surveyed correctly identified potential risk of neuropsychiatric symptoms with Chantix use in the three survey items pertaining to these symptoms.

In June of 2009, FDA issued further guidance for the postmarketing requirement through extensive internal discussion. It was determined that only a randomized controlled trial would be suitable to evaluate the risk of neuropsychiatric adverse events with varenicline because the outcome could not be reliably detected in the coded data, such as the types that would be available for observational studies.

FDA recommended the trial be a large randomized, double-blind active and placebo-controlled trial with treatment arms including varenicline, bupropion, nicotine replacement therapy, and placebo. It should compare the risk of clinically significant neuropsychiatric adverse events, including but not limited to suicidality.

An additional goal would be to determine whether individuals with a prior history of psychiatric disorders are at a greater risk for development of clinically significant neuropsychiatric adverse events compared to individuals without a prior history of psychiatric disorders.

The primary endpoint for the postmarket required trial was custom crafted to capture the scope of neuropsychiatric adverse events that have been reported by patients taking varenicline. A certain severity of symptoms is required for some symptoms because of the recognition that some neuropsychiatric symptoms occur with smoking cessation.

The primary endpoint is a composite of the following events: the occurrence of at least one treatment-emergent severe adverse event of anxiety, depression, feeling abnormal, or hostility, or the occurrence of at least one treatment-emergent moderate or severe adverse event of agitation, aggression, homicidal ideation, delusions,

hallucinations, paranoia, psychosis, mania, panic, suicidal ideation, suicidal behavior, or completed suicide.

Interim analyses of the randomized controlled trial results were planned to ensure an adequate number of outcome events were observed. In order to move ahead with the plan for a total of 8,000 patients randomized with 2,000 per treatment arm, the blinded outcome incidence needed to be greater than or equal to 3.5 percent in these interim analyses.

The first interim analysis occurred at about half enrollment, when 4,000 patients completed the week 20 visit. The incidence of the blinded primary endpoint was about 4 percent. The second interim analysis occurred at about three-quarters enrollment, when 6,000 patients had completed the week 20 visit. The incidence of the blinded primary endpoint was 4.5 percent.

This study completed enrollment of all 8,000 patients this past summer, and Pfizer anticipates submitting the final study report in the third

quarter of 2015.

I have just given FDA's overview of the regulatory history regarding neuropsychiatric adverse events with varenicline. I want to review the remaining presentations you will hear today.

Next, there will be an FDA overview of guidelines and regulations regarding boxed warnings and warning statements. The next presentation will be Pfizer's presentation. Following that, there will be an FDA presentation of the clinical perspective on neuropsychiatric adverse events associated with varenicline, then the FDA evaluation of the Pfizer-conducted meta-analyses and FDA's review of the observational studies submitted by Pfizer.

Following these presentations and the open public hearing, we will ask you to consider the evidence presented today and make a recommendation about how best to describe the risk of neuropsychiatric adverse events in varenicline labeling. Your response to our questions, and especially your discussions that will form the

foundations for those responses, will be critical to us as we consider how to approach any additional regulatory actions for varenicline.

Before we move on to the day's presentations, I'd like to preview the questions we'll be discussing later. The first is a discussion question. Please discuss how you weigh the evidence contributed by the randomized controlled trial meta-analyses, observational studies, and spontaneous case reports when evaluating the risk of serious neuropsychiatric adverse events and patients taking varenicline.

The next question is a voting question and a discussion question. Based on the data presented on the risk of serious neuropsychiatric adverse events with varenicline, what would you recommend? A, removal of the box-warning statements regarding risk of serious neuropsychiatric adverse events, B, modification of the language in the boxed warning, or, C, retain the current boxed warning statements and reassess once the ongoing postmarketing randomized controlled trial designed to capture

serious neuropsychiatric adverse events is completed.

That would be followed with an explanation of the rationale for your answer and discussion of any additional actions you think the agency should take regarding the risk of serious neuropsychiatric adverse events with varenicline.

Thank you again for your participation in this important meeting. We look forward to the discussions.

FDA Presentation - Eric Brodsky

DR. BRODSKY: Good morning. Welcome to the Washington, D.C. area, and welcome to the FDA's White Oak campus. I'm Eric Brodsky from the SEALD labeling team in the Office of New Drugs.

So one of the tasks for this advisory committee meeting is to provide recommendations to the FDA about how to communicate in labeling the possible risks of serious neuropsychiatric events associated with varenicline; so more specifically, as Dr. Racoosin stated, whether to remove the boxed warning, whether to modify the boxed warning, or to

retain the boxed warning and wait for the results of the 8,000-patient postmarketing trial that will be available in about a year.

Thus, it is useful to provide a regulatory framework by the regulatory requirements and the guidance recommendations for the warnings and precautions section and the boxed warning sections of the prescribing information.

Today, I will talk about the requirements for the prescribing information and, as I stated, the regulatory requirements and the guidance recommendations for the warnings and precautions section, and the boxed warning sections of the prescribing information.

Specifically, I will review the criteria outlined in the warnings and precautions section -- sorry, the warnings and precautions guidance criteria to include a boxed warning. I will also discuss possible reasons for removing a boxed warning. Finally, I will provide an example of when a boxed warning was removed.

So the prescribing information is geared for

the healthcare provider. It's written for the healthcare provider, and it must contain a summary of the central scientific information needed for the safe and effective use of a drug. It must be informative and accurate, and it must not be promotional, false, or misleading.

The prescribing information is a living document, and it changes all the time. It must be updated when new information becomes available that causes the labeling to become false, inaccurate, or misleading.

So the warnings and precautions section should describe serious or clinically significant adverse reactions that occur with a drug or risks that are expected to occur.

For the purposes of labeling, adverse reactions or untoward events that are associated with the drug with a possible causal relationship to the drug, and for the purposes of labeling, serious adverse events are adverse events that are life-threatening, result in hospitalization, prolonged hospitalization, significant disability,

a fatality, or a congenital abnormality, each warning and precautions section should include a succinct description of the clinically significant adverse reaction, or serious adverse reaction, or risk, and should include the description of the adverse reaction or risk: who's at risk, what happens to these patients or the outcome, the estimate of the risk or the adverse reaction rate, and steps to prevent, monitor, or manage the adverse reaction, if known.

According to the regulations, the FDA may require a boxed warning for certain contraindications or serious warnings, particularly those that may lead to death or serious injury. For the purposes of labeling, a contraindication is a situation or subpopulation in which the risk always outweighs the benefit. One must not use the drug.

According to the regulations, the boxed warning section must be the first section in the full prescribing information. It also must be surrounded by a physical box, a single black line,

which surrounds the warning information.

According to the warnings and precautions guidance, typically, boxed warnings are used for three situations.

Adverse reactions that are so serious in proportion to potential benefit that it is essential to be considered in assessing the risks and benefits of using a drug.

Number two, there's a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug. So situations of appropriate use would be potentially a contraindication, a limitation of use, avoiding the use of a drug with a concomitant medication, a dosage modification, or monitoring. So this is the reason why the varenicline boxed warning was inserted.

Another typical reason a boxed warning is included, according to the warnings and precautions guidance, is that the drug is approved with a restriction for use, so restrictions to assure safe use because the drug can only be safely used if

distribution or use is restricted.

So for example, if a product is approved within an ETASU, an element to assure safe use, with a restricted distribution under risk evaluation and mitigation strategies, that warning is included in the boxed warning.

Now, those are the three typical reasons a boxed warning is included. However, the guidance, the warnings and precautions guidance, states other reasons can be used to include a boxed warning. So there is some flexibility about the inclusion criteria for a boxed warning.

Other reasons include to highlight a warning that is especially important to a prescriber or potentially if there's a drug that poses a risk/benefit considerations that are unique among drugs in the class. For example, if a drug is potentially a second-line agent because of a safety reason, this may be a reason to highlight that in the boxed warning.

So with respect to removal of boxed warnings, there's no law, no regulation, no

guidance that specifically has rules for removing a boxed warning. However, if the criteria for a boxed warning, as I discussed, as outlined in the warnings and precautions guidance, are no longer present, it is reasonable to assume that potentially one could remove a boxed warning.

So boxed warnings are typically not commonly removed. More commonly, they are modified to be consistent with PLR recommendations, the warnings and precautions guidance. However, when boxed warnings have been removed, typically, the criteria are no longer met.

So I'm going to provide one example of when a boxed warning was removed. Rosiglitazone, a medication approved for type 2 diabetes with diet and exercise, is a specific example. In June of 2007, there was a retrospective published meta-analysis of 42 controlled trials, mostly of six-month duration, that showed a potential increase of myocardial infarction associated with rosiglitazone over comparators metformin and sulfonylureas.

Later in that year, the myocardial infarction boxed warning was added to the prescribing information for rosiglitazone because the myocardial infarction was felt to be so serious in proportion to the benefit of the drug, and MI potentially could be prevented by appropriate use of the drug.

I should note this was the second boxed warning for this product, so the MI boxed warning was added in addition to the congestive heart failure boxed warning.

Subsequently, RECORD, which was a prospectively designed cardiovascular outcome trial, which compared the cardiovascular safety of rosiglitazone to comparators metformin and sulfonylurea, was completed in 2009. These results were presented at an advisory committee in 2010. The results were challenged. This resulted in FDA requiring a re-analysis, a re-adjudication of the outcome trial to assess the myocardial infarction signal.

So after re-adjudication of RECORD, the MI

rate was not significantly increased in the rosiglitazone group compared to the active controls, metformin and sulfonylurea. So essentially, the results from RECORD contradicted or were inconsistent with the results from the meta-analysis. Because of that, the criteria for the boxed warning were no longer met, so the myocardial infarction boxed warning was removed. Thank you.

DR. PARKER: Thank you.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel

expenses, honoraria, and interest in the sponsor, including equity interest and those based upon the outcome of the meeting. Likewise, FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will proceed now with the sponsor's presentations. Thank you.

Industry Presentation - Christopher Wohlberg

DR. WOHLBERG: Thank you, Dr. Parker.

Good morning. My name is Christopher Wohlberg. I'm the safety group head for global innovative pharma at products at Pfizer. I'd like to thank the advisory committee members and the FDA for allowing us an opportunity to present the current data regarding the neuropsychiatric safety of varenicline.

During our presentation today, we will

briefly review events leading up to the boxed warning on the Chantix label, which was based on a safety signal arising from postmarketing reports of serious neuropsychiatric events. We agree with the division that postmarketing reports regarding serious neuropsychiatric events constituted a safety signal in 2007 and 2008.

However, the aggregate data now available from 18 randomized clinical trials and 4 independently conducted observational studies do not appear to validate that concern. We will show you these results today, and we will show you how the results of these studies and meta-analyses thereof have recently been incorporated into the Chantix label.

In light of the data to be presented today and based on the 2011 FDA guidance regarding the use of boxed warnings, the currently available evidence is inconsistent with such a warning. The key issue for this committee to decide is whether the risk of serious neuropsychiatric events shall also remain as a boxed warning, the highest level

of warning available to the FDA.

We believe that the recent revisions to section 5.1, the warnings and precautions section of the label, are adequate and sufficient to describe the emergence of serious neuropsychiatric events in patients who are quitting smoking.

Our presentation will consist of three parts. Following my introductory presentation, Dr. Samuels will describe how the safety signal derived from postmarketing reports was assessed with additional randomized clinical trials and, further, where and how the results of these studies and additional analyses have been added to the Chantix warnings and precautions section.

Dr. Robert West from the Department of Epidemiology and Public Health, University College London, will describe how the results of four large independent observational studies are convergent with the results from these clinical trials.

We know health consequences of smoking and tobacco use are clear. Smoking kills. Virtually every organ system in the body can be affected by

smoking, as shown in this graphic from the Surgeon General's report.

Cigarette smoking causes more than 480,000 deaths per year in the United States, and that's about 1 in 5 deaths. Smoking causes more deaths each year than HIV, illegal drug use, alcohol use, motor vehicle accidents, and firearm-related deaths combined. About 80 percent of COPD cases and 90 percent of lung cancer cases are caused by smoking. And finally, more than 10 times as many U.S. citizens have died prematurely from smoking cigarettes than have died in all of the wars fought by the United States in its entire history.

As described in the Chantix boxed warning, the health benefits of quitting smoking are immediate and substantial. Within 24 hours, decreases in blood pressure and pulse rate are noted. Within one year, the excess risk of cardiovascular disease is cut in half. And after 10 to 15 years, quitting smoking results in substantial decreases in the risk of lung cancer, stroke, and coronary artery disease.

Varenicline was developed specifically to target the receptors thought to be responsible for the addictive properties of nicotine. Nicotine receptors are widely distributed in the brain, and one of these, a subtype known as the alpha 4 beta 2 receptor, located in the ventral tegmental area, is thought to be responsible for the craving and reward mechanisms of nicotine mediated by phasic dopamine release in the nucleus accumbens.

Varenicline is a partial agonist, that when compared to nicotine has a higher binding affinity to the alpha 4 beta 2 receptor, yet produces less dopamine release. This partial agonism may allow a smoker to get some, but not all of the pleasurable effects of nicotine, which reduces some of the reward associated with smoking and mitigates some of the withdrawal effects when a smoker tries to quit. Further, through occupancy of the alpha 4 beta 2 receptor, varenicline also inhibits the full agonist effect of nicotine during a relapse.

At therapeutic concentrations, which range from approximately 20 to 60 nanomolar, varenicline

is highly selective for the alpha 4 beta 2 receptor and does not appreciably bind to receptors that are thought to play a role in psychiatric disorders shown in the bottom right half of the slide.

Varenicline may bind, to some degree, on other nicotinic acetylcholine receptors at therapeutic concentrations. And this may provide an explanation for the effects seen on sleep, as the cholinergic system is involved in both rapid eye movement sleep as well as cortical arousal.

If the pharmacology of varenicline does not suggest a risk of neuropsychiatric events, are there other potential explanations for the emergence of these events?

In 2004, the results of the National Epidemiologic Survey on Alcohol and Related Conditions was published in the Archives of General Psychiatry. The 12-month prevalence of Axis I and Axis II disorders was found to be increased in nicotine-dependent adults compared to those not dependent on nicotine. The primary Axis I diagnoses included drug and alcohol use disorders,

major depression, and anxiety disorders. Personality disorders, shown in the bottom row, were the most common Axis II diagnoses in a survey of 43,000 adults in the general population.

In addition, smokers are also more likely to experience suicidal ideation and behavior, even when controlling for depression. The incidence of suicidal ideation by smoking status was estimated using data from the Baltimore Epidemiologic Catchment Area follow-up study.

This is a longitudinal community cohort study with 23 years of follow-up. Face-to-face structured interviews were designed to identify incident cases of mental disorder, defined by DSM criteria, and were conducted in 1981, '82, '93, and 2004.

This slide shows the age-adjusted incidence of first-ever occurrence of suicidal ideation among current smokers shown in purple, former smokers in blue, and never-smokers in orange. The bars on the left depict the incidence among those with no history of depression. The bars on the right show

the incidence among those with a history of depression.

Among both groups, current smokers have the highest risk of suicidal ideation relative to former and never-smokers. The increased risk of suicidal ideation among smokers remains after controlling for a prior history of depression.

Also, consider that quitting smoking is commonly associated with withdrawal symptoms. These symptoms shown on this slide are described in DSM-V and include irritability, frustration or anger, anxiety, difficulty concentrating, increased appetite, restlessness, depressed mood, and insomnia.

Withdrawal symptoms may occur in approximately half of the smokers who quit for two or more days. The average duration of these withdrawal symptoms is two to three weeks, but as reported by Weinberger, et al., the duration of withdrawal symptoms may be prolonged in patients who have major depression and/or alcohol or substance abuse, and this interaction is stronger

in women.

When studied in an uncontrolled manner, increased reporting of events that are commonly seen in the population being studied is termed indication bias. I'll examine other biases inherent in case reports later, but it's important to begin considering that these biases can have significant impacts on our ability to determine causality, as we'll now explore.

This slide compares some of the characteristic strengths and weaknesses of the three major sources of safety data. They all differ in the degree of diversity in the patient population, whether or not the incidence rates can be estimated, the availability of comparator groups, and the typical quality of information received.

Although each are different, each source of safety information plays a critical role in understanding the safety profile of the medication, and postmarketing data can be useful in identifying new safety signals that may not have been

previously observed.

As you will see, we will devote most of this presentation to clinical safety data, and as we review that information, it would be helpful to keep these key pharmacovigilance definitions in mind.

The Counsel for International Organizations of Medical Sciences, or CIOMS, working group 4, defines a safety signal as a report or reports of an event with unknown causal relationship to treatment that is recognized as worthy of further exploration and continued surveillance. Signals generate hypotheses to be tested with more rigorous methods, including randomized clinical trials, observational studies, and that the biases and limitations can be controlled in both of these types of data.

As described in the FDA final rule, published in 2010, an adverse event, the next row, is an untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Moving on, a suspected

adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the adverse event. CIOMS working group 6 suggested that reasonable possibility should mean that there are facts, evidence, or arguments to support a causal association with the drug.

Finally, an adverse reaction is a subset of all suspected adverse reactions for which there is a reason to conclude that the drug caused the event. These definitions are relevant specifically to the appropriate use of a boxed warning, as you can see, by considering the FDA's 2011 guidance on the topic.

Boxed warnings are the highest level of warning and are typically reserved for the most serious adverse reactions. There are several scenarios, as you've heard already, that are listed in this FDA guidance, published in October 2011, in

which boxed warnings are generally described as appropriate. These scenarios describe serious adverse reactions and the need to appropriately select and/or monitor patients.

As you can see, the definition of adverse reaction is very relevant to the consideration of the appropriate use of a boxed warning. These warnings generally are used when there is reason to conclude that there is a causal association between the drug and the event.

In contrast to boxed warnings, the guidance regarding warnings and precautions allows for descriptions of adverse reactions and other potential safety hazards where a causal relationship need not have been definitively established between the drug and the event.

We agree with the FDA that all smokers who are attempting to quit should be monitored for the emergency of serious neuropsychiatric events, but as we will show you, the data do not support including such a warning in a box.

At the time that the FDA approved Chantix in

2006, the understanding of varenicline safety profile was primarily derived from phase 2 and 3 clinical trials. These data were limited in certain respects by the small number of patients with a history of psychiatric diagnoses who are allowed to participate in those trials.

The clinical database available in 2009 included 10 placebo-controlled trials and over 3,000 patients who had been treated with varenicline, as shown on the left side of the slide. The information on the right half of the slide will be the subject of Dr. Samuels's and Dr. West's presentation today.

A meta-analysis was conducted of these 10 placebo-controlled trials, available in 2009. The slide shows the risk ratio for the MedDRA high-level group terms in the psychiatric system organ class. With the exception of sleep disturbance and disorders, all of the 95 percent confidence intervals included one, and the overall risk ratio for emergence of psychiatric symptoms was 1.02.

Following varenicline's approval, spontaneous reports of neuropsychiatric events received during the first years of launch raised concerns about the emergence of serious neuropsychiatric events in patients treated with varenicline. We agreed with FDA that these reports constituted a safety signal.

Like all products in our portfolio, postmarketing safety is assessed for these products on an ongoing basis. And the methods and frequency of surveillance for varenicline are shown on this slide. We consider postmarketing pharmacovigilance to be a very important component of understanding product safety, and these reports may generate safety signals for events that were not identified during clinical trials, particularly those that are rare.

For instance, varenicline's spontaneous reports receive early after market introduction were used to identify and confirm a signal for hypersensitivity reaction and severe skin reactions. However, as we discussed earlier, all

data sources have their inherent limitations including postmarketing spontaneous reports.

Some of these include adverse event recognition. It's not required that causality be established in order to report an event. Underreporting is commonly known to occur. There is indication bias, as I have already described. There are other reporting biases inherent in postmarketing reports. And then there's the estimation of exposure, in which it is generally impossible to know the true incidence of events from postmarketing data.

Based primarily on postmarketing reports, FDA implemented a boxed warning in July of 2009. As indicated here, several events involving media publicity, regulatory announcements, and label revisions occurred during the period over which adverse reporting increased.

For example, in early September 2007, the fatal shooting of a musician in Texas who was taking varenicline was highly publicized in the media. Subsequent to this, FDA and European Health

Authority communications and announcements about varenicline labeling revisions occurred, as indicated in the boxes.

Based on their close temporal relationship, we believe that these events contributed to the increase seen in postmarketing reporting in serious neuropsychiatric adverse events beyond the baseline level seen prior to September 2007. As noted in the FDA briefing document, this is an example of stimulated reporting.

Shown here is the current boxed warning for Chantix. At the time that the boxed warning was added to the label, the FDA indicated that the intent was to encourage close monitoring of patients and not to discourage use of smoking cessation products.

However, Bradford and Clay recently published an article examining the impact of boxed warnings on utilization in which they examine prescribing patterns for non-steroidal pain medications as an example. They found that even when controlling for various sources of

information, boxed warnings still had a significant impact on prescribing.

Additionally, the combination of media attention and regulatory actions led to a differential impact on prescribing, with those products receiving the negative media attention showing the greatest decline in utilization. And in fact, those that did not, even though the boxed warning was uniform, saw an increase in prescribing.

More specifically, warnings regarding serious neuropsychiatric events have changed the prescribing behaviors for smoking cessation products in the U.K. Huang, et al. reported in BMC this month about the pattern of usage of smoking cessation products using association-rule mining to analyze data on prescribing patients among approximately 480,000 patients in a thin database. The authors found that varenicline was most commonly prescribed in heavy smokers aged 31 to 60 years who are otherwise healthy and sometimes in patients with COPD.

They further note, although both BMF and NICE guidelines suggest that the risks of smoking cessation aids are best managed by monitoring and not by non-use, concerns regarding adverse events have resulted in decreased utilization in patients with depression, anxiety, psychotic disorders, and dementia.

The authors concluded, since continued smoking carries a more substantial health risk for the great majority of these individuals, this practice may be counterproductive to individual and public health.

In addition to an impact on prescribing patterns and as shown on this slide, perceptions regarding drug risk may impact how adverse events are reported. Dr. Prochaska, present today on our panel, described how serious adverse events from three randomized studies of in-patients with mental illness are reported.

In these trials of NRT, nicotine replacement therapy, in patients with serious mental illness, over 3,500 serious adverse events were reported in

1280 patients treated with NRT. None of these SAEs were considered related, including 39 deaths, of which there were 9 suicides and 3 homicides. And although all of these events were reported to the DSMP, none were reported by the investigators to FDA.

However, there were a few patients in these same NRT studies who reported taking varenicline prior to hospitalization. Because of the perceived risks of varenicline, reporting of these events was discussed in each case with a treating clinician, even if the patient was not enrolled in the NRT study.

Furthermore, in a separate, small study, 17 patients involving varenicline, 2 hospitalizations were reported as serious cases by investigators to the FDA, even though one was a prescheduled hospital admission that would not typically meet criterias in SAE. This differential pattern of reporting is termed notoriety bias.

As noted on this slide, there has been a general trend of increased adverse event reporting

of all types over time. As concluded by the authors, all things being equal, a drug marketed in more recent years is more likely to have cases that mention it. As it applies to comparisons of products over time, this is termed temporal bias.

When there's a general increase in reporting over time, this should not affect disproportionality assessments. However, non-random increases in reporting in the absence of stratification could impact disproportionality results for the products approved at different times.

Since the boxed warning, utilization of all smoking cessation products has decreased, as noted in the FDA briefing document, but the impact on varenicline utilization was greater than for OTC products. Now, does this matter?

A network analysis was conducted by the Cochrane Group, demonstrating that in comparison to other monotherapies, varenicline was statistically superior to placebo, bupropion, and nicotine replacement therapy.

This slide shows the odds ratio for successful quitting. Point estimates to the right of 1 favor the index drug, the first drug listed, over the comparison drug or the second drug listed. It can be seen that the odds ratio for varenicline is statistically superior to placebo, bupropion, and NRT in this analysis, while bupropion and NRT had essentially an equal chance of successful quit attempts. Because varenicline is the single-most effective smoking cessation, warnings about its risks that are not supported by the available evidence may have unintended consequences.

Achieving abstinence from smoking is the single most important thing that we can do for our patients. And given the substantial benefits of quitting smoking, it's reason to estimate the incremental benefit of varenicline compared to treatment alternatives on health outcomes. The benefits of smoking cessation on outcomes model is one way to estimate the impact of differential efficacy on smoking-related morbidity and mortality outcomes.

This model simulates the health outcomes of a hypothetical cohort of adult smokers who make a single attempt to quit smoking either unaided or with varenicline, bupropion, or NRT. The entire cohort is assumed to use the same intervention for the attempt and the resulting impacts on smoking-related morbidity and mortality from four smoking-related conditions, COPD, cancer, coronary artery disease, and cerebral vascular disease are then compared.

The results of these comparisons with varenicline are presented here in a cohort size of 1 million smokers who attempt to quit. The top three rows estimate the two-year and lifetime impact on mortality while the bottom three rows show the impact on excess smoking-related morbidity.

The results of this model support the intuitive conclusion that the most effective aid to smoking cessation presents the best opportunity to reduce the health burden of smoking.

As noted by Dr. Evins, also on our panel

today, in her commentary in the American Journal of Psychiatry, case reports and postmarketing pharmacovigilance reports are critical sentinels that identify adverse events possibly associated with medical treatments in a real-world practice, not seen in carefully selected samples and randomized controlled trials that could change the risk-to-benefit assessment of treatment and general practice. But because of reporting bias, confounding, multiple reporting and uncertain denominator inherent in these reports, controlled trials are essential to determine whether a causal association exists.

I have shown examples of indication bias, temporal bias, and notoriety bias in this introduction. The factors can be minimized with appropriate clinical trial design and corrections in observational studies. Safety concerns raised by the postmarketing reports that led to the boxed warning were evaluated utilizing additional randomized clinical trials in large, independent observational studies.

Dr. Lawrence Samuels will now present the results of the randomized controlled clinical trial safety data.

Industry Presentation - Lawrence Samuels

DR. SAMUELS: Good morning. My name is Lawrence Samuels. I'm the medical affairs Chantix lead for Pfizer.

As previously noted, the boxed warning regarding neuropsychiatric events on the Chantix label was based on a safety signal from postmarketing reports. Since the addition of the boxed warning, controlled clinical trial data and observational data have been generated to test this hypothesis of whether neuropsychiatric events are causally related to varenicline.

In my presentation, I will review the data from controlled clinical trials, and Dr. West will follow and present the results from independently-sponsored observational studies.

We believe that the totality of data that will be reviewed with you today will show that there is a convergence of evidence from placebo-

controlled studies, meta-analyses, and observational studies that is remarkably consistent and shows no evidence of an increased risk of neuropsychiatric adverse events, other than sleep disorders, in smokers treated with varenicline compared with smokers treated with placebo or other smoking cessation pharmacotherapies.

This slide provides an overview of the clinical trial program for Chantix, broken down by the time frame when the studies were conducted. The middle rows are the 8 clinical studies that had been completed since 2009, when the boxed warning was added.

The studies are listed using abbreviated study names as well as the Pfizer study number, and in referring to these studies, I will use these abbreviated names or study numbers. The number of subjects in each study by treatment group is shown in the middle column, and the column on the right shows the acronyms for the psychiatric scales that were included in the studies to assess neuropsychiatric events.

There is a total of 18 Pfizer-sponsored placebo-controlled studies that include more than 5,000 varenicline-treated subjects compared to almost 3,500 placebo patients.

Among the studies conducted since 2009 are two studies that enrolled subjects with past or current psychiatric diagnoses, one in subjects with major depressive disorder and one in patients with schizophrenia or schizoaffective disorder. Five studies highlighted here included the use of the Columbia Suicide Severity Rating Scale to assess suicidal ideation and/or behavior. This scale is widely used and has been recommended by the FDA as well as other international organizations.

Meta-analyses of neuropsychiatric adverse events from 18 studies and a meta-analysis of suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale from five studies has also been conducted.

In addition to the completed studies, as mentioned earlier, there is a large neuropsychiatric safety study, Pfizer study 1123,

that is currently ongoing. This study was designed in collaboration with the FDA to assess neuropsychiatric safety of varenicline versus placebo, NRT patch, bupropion in smokers with and without psychiatric disorders, and this study is expected to read out in third quarter of 2015.

There will be a total of 8,000 subjects entered into the trial, 2,000 subjects in each of the four treatment groups. Of the 2,000 subjects in each group, 1,000 will have a diagnosis of psychiatric disorder and 1,000 will not. The primary endpoint, which was presented earlier, is a composite of moderate to severe neuropsychiatric adverse events.

At this time, the enrollment is complete and there have been two interim analyses conducted, the first at 50 percent of enrollment and the second interim analysis, which included data from 75 percent or about 6,000 randomized subjects, which was completed earlier this year. This interim analysis was blinded for the sponsor, but unblinded for the independent data monitoring

committee.

Following completion of the interim analysis, the data monitoring committee, which reviewed actual and projected neuropsychiatric adverse event rates for each of the four treatment arms to establish if the planned sample size of 8,000 was sufficient, they recommended to continue the study to the original target of 8,000 subjects. The blinded rate of primary neuropsychiatric adverse events of the primary endpoint of the total population was 4.5 percent.

Now, the results of this study will be important in further characterizing the psychiatric safety of varenicline. However, we believe that the currently available data, which will be presented to you today, are sufficient to address whether a boxed warning is appropriate for varenicline.

I'll start by reviewing the results from the two clinical studies that assess varenicline and the treatment of smokers with a psychiatric disorder. In the first study, published by

Anthenelli, et al., in the Annals of Internal Medicine, varenicline was studied in smokers with major depressive disorder. The population included smokers with current or past diagnoses of depression who are on stable antidepressant treatment or had a successfully-treated depressive episode in the previous two years.

Now, in this study, about 70 percent of the population were on a stable antidepressant treatment. This randomized double-blind placebo-controlled study included several psychiatric scales to assess the neuropsychiatric safety of varenicline, including scales to measure depression, anxiety, and suicidal ideation, and behavior.

This table lists the number of subjects with psychiatric adverse events that occurred at a rate greater than or equal to 1 percent in either of the treatment groups. Adverse events that were reported in this study were coded to MedDRA, and this slide lists the adverse events within the psychiatric disorder system organ class. The high-

level group terms are shaded in gray, and the preferred terms are listed under their respective high-level group terms.

The most common psychiatric adverse events were sleep disorders, shown on the top line, which primarily includes abnormal dreams and insomnia. The rate of sleep disorders was higher in the varenicline group versus the placebo group. This increase in sleep disorders is consistent with what we had previously seen in varenicline studies in smokers without a psychiatric disorder.

The incidence of other psychiatric adverse events, including anxiety disorders, depressed mood disorders, or other mood disorders were generally similar between the two treatment groups. Suicidal ideation or behavior was actually higher in the placebo-treated group, 5 patients versus zero in the varenicline group.

Personality disorder, which primarily includes hostility, was higher in the varenicline patients versus placebo. And the next slide provides additional information regarding these 5

hostility events. Of the 5 hostility events, 3 were mild, 2 were moderate, none were serious, none resulted in a discontinuation from treatment. Four of these events occurred during the treatment period and there was no pattern of onset or duration.

Results from the psychiatric rating scales measuring depression and anxiety are shown on this slide. This slide shows the mean change from baseline for the MADRS rating scale on the left, which measures symptoms of depression, and the HAM-A rating scale on the right, which measures anxiety symptoms. For both scales, positive changes indicate more symptoms and negative changes indicate improvement.

The baseline scores for both the MADRS and the HAM-A scales were similar between varenicline and placebo, and they showed that depression symptoms and anxiety symptoms were generally mild. For both depression symptoms and anxiety symptoms, the results show that there were actually slight improvements over the 12-week treatment period in

both varenicline and placebo patients. And the mean depression and the mean anxiety changes from baseline were actually similar between the varenicline and placebo treatment groups.

This slide shows the results using the Columbia Suicide Severity Rating Scale. As shown on the top line, about a third of the subjects in this trial had a previous lifetime history of suicidal ideation or suicidal behavior.

During the treatment period, outlined in green, the rate of suicidal ideation or behavior was similar between the varenicline and the placebo groups. The rates of suicidality were similar between the treatment groups also during the post-treatment period, that is more than 30 days after the last dose of treatment.

We also studied varenicline in smokers with schizophrenia or schizoaffective disorder. And the objective of this trial, which was published by Williams, et al., in the Journal of Clinical Psychiatry, was to assess the neuropsychiatric safety of varenicline in this patient population.

This was a randomized 2 to1, varenicline to placebo, double-blind placebo-controlled study that included psychiatric rating scales to measure schizophrenia symptoms as well as the Columbia Suicide Severity Rating Scale to assess suicidal ideation and behavior.

All subjects that were entered into this trial were diagnosed using a structured clinical interview. This study included 84 subjects treated with varenicline and 43 treated with placebo. Now, because of the relatively small size of this trial, the psychiatric adverse events that are shown on this slide are shown by preferred terms that were reported in two or more subjects.

As shown in the top line, the overall rate of psychiatric adverse events in the varenicline group was 36.9 percent versus 32.6 percent in the placebo group. There were some differences in certain adverse events between these groups. For example, auditory hallucination and insomnia occurred at a higher rate in the varenicline group, whereas abnormal dreams, anxiety, and depression

occurred at a higher rate in the placebo group. The rate of suicidal ideation was similar between the two groups.

There was one suicide attempt by a varenicline-treated patient who had a lifetime history of similar attempts, and I will address this issue of varenicline and suicidal ideational behavior when I present the results of the meta-analyses in a few moments.

Results of the PANSS rating scale using total score are shown on this slide. This rating scale measures the severity of schizophrenia symptoms. As shown on the graph on the left, the mean total scores at baseline were comparable between varenicline and placebo and reflect an average rating corresponding too mild symptoms.

Over the 12-week treatment period as well as the follow-up period up to week 24, the total PANSS score remained stable with modest decreases observed in both groups, indicating no worsening of psychiatric symptoms.

As shown on the right, each of the subscales

for positive symptoms as well as negative symptoms are shown, and they show similar ratings scores between varenicline and placebo.

Results of the Columbia Suicide Severity Rating Scale are shown here in this slide. The top line shows that there was actually a higher proportion of subjects that were assigned to the varenicline group who had a lifetime history of suicidal ideation or behavior. Despite this imbalance, the incidence of suicide-related events was similar between the two treatment groups during the treatment period, as shown in the green box.

As shown on the last line of the table, there was a high proportion of subjects in the varenicline group that reported suicidal ideation or behavior after the end of treatment, that is more than 30 days after the last treatment dose, compared to placebo. And we believe this is a result of the imbalance of patients with a lifetime history of suicidality that were assigned originally to the varenicline treatment group.

Of these 8 subjects in the varenicline group

that answered yes in the post-treatment follow-up, all were for suicidal ideation and 7 of the 8 did have a lifetime history of suicidal ideation.

Now, given the strengths and limitations of these studies, we can conclude that there was actually no worsening of either schizophrenia symptoms or depression symptoms in the varenicline group versus placebo group, as measured by psychiatric scales. In addition, there was a similar proportion of subjects in the varenicline and placebo groups who reported suicidal ideation or behavior, as assessed by the Columbia Suicide Severity Rating Scale.

Now, with this data, in patients with psychiatric illness, the Chantix label has been updated and no longer states that the safety and efficacy of Chantix in such patients has not been established. As shown here, the label now reads, "Limited safety data are available from postmarketing smoking cessation studies in two patient groups, patients with major depressive disorder and patients with schizophrenia or

schizoaffective disorder."

Now, to address the limitation of the size of individual studies, meta-analyses of placebo-controlled studies were conducted to further evaluate the neuropsychiatric safety of varenicline. And I will review the results of a meta-analysis of psychiatric adverse events in 18 placebo-controlled studies as well as a meta-analysis of 5 placebo-controlled studies that assess suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale.

A meta-analysis of psychiatric adverse events, which were coded to the high-level group terms within the psychiatric disorders system organ class, was conducted, as I stated, based on 18 placebo-controlled studies. There was a total of 5,072 varenicline subjects and 3,449 placebo subjects that were included in this analysis. And this analysis includes two of the studies, as I just presented, that included patients with a diagnosis of a psychiatric disorder.

In this slide, the number of patients with

adverse events, included in the psychiatric system organ class, are listed by high-level group term in descending order by frequency within the varenicline group. Risk ratios and 95 percent confidence intervals are shown for the high-level group terms in the right-hand column. For risk ratios, a confidence interval that includes 1 means that there is no significant difference between the two treatment groups.

The high-level group terms listed or highlighted are those where the confidence interval did not include 1. Sleep disorder, highlighted in yellow, was the most frequently-recorded adverse event.

Also, it was the only psychiatric adverse event that was higher in the varenicline group versus placebo and the confidence interval did not include 1, suggesting varenicline is associated with an increased risk for sleep disorders. It should be noted that sleep disorders are also associated with nicotine as well as nicotine withdrawal.

Suicidal behavior, highlighted in purple, was lower in the varenicline group, and the confidence interval did not include 1. This finding supports, however, the conclusion that varenicline does not increase the risk of suicidal ideation or behavior.

Additional information regarding varenicline and suicidality will be discussed further when I present the results of the meta-analysis of five studies that included the Columbia Suicide Severity Rating Scale.

Now, for the other psychiatric adverse events, the risk ratios were actually similar between varenicline and placebo, and the 95 percent confidence interval included 1, meaning there was no difference between varenicline and placebo-treated subjects.

Personality disorders, which does not represent an Axis II diagnosis but is a MedDRA term that includes adverse events of aggression and hostility, was numerically higher in the varenicline group, although the confidence interval

did include 1. And I'll come back to this observation in a moment.

This slide shows the high-level group term events from the previous slide in terms of time to first onset by study week, and the data are presented for varenicline-treated subjects as placebo-adjusted rates, subtracting out the placebo rates. The results are consistent with that shown in the previous slide and show that only sleep disorders are increased above zero.

In addition, there was no temporal pattern of emergent events with the exception of sleep disorders, which largely occurred during the first four weeks of treatment.

Now, as described earlier, there was a numerically higher rate of personality disorders and disturbances in the varenicline group, although the confidence interval did include 1, and I want to review with you what we know about this observation.

Now, as shown in the next slide, the difference was driven in large part by difference

in hostility events. This slide shows the preferred terms that are included in the personality disorder high-level group term. And as shown here, both varenicline and placebo had similar rates of aggression, .2 percent. There were 6 events of hostility in the varenicline group versus 1 event in the placebo group.

Now, of these six events, five were from the depression study, which I discussed earlier. In order to look at the clinical relevance of the events of hostility, which occurred across the 18 clinical studies, we conducted a meta-analysis using the standardized MedDRA query, or SMQ, to look at all the adverse event terms, which are similar to hostility.

This slide shows the risk differences for the hostility aggression SMQ. And I show the risk difference rather than risk ratio in order to show all the studies, even those that have zero events in one of the treatment groups.

As seen here, hostility was higher in the depression study, that is Pfizer study 1122,

highlighted in yellow. It was lower in Pfizer study 1028, one of our pivotal trials, highlighted in purple. In all the other studies, as well as in the overall analysis on the bottom line, there was no evidence of increased risk of hostility versus placebo.

This slide shows the results of the meta-analysis of all combined psychiatric adverse events, excluding sleep disorders and disturbances, which is, as I mentioned earlier, a known adverse event associated with varenicline. The middle columns show the absolute number of events and incidence rates for the endpoint as measured for each treatment group.

The risk ratio and 95 percent confidence intervals are shown on the right-hand column. The top line shows the results for any psychiatric adverse event other than sleep disorders and shows that there was no increased risk of psychiatric adverse events for varenicline versus placebo, with a risk ratio of 1.01 and a confidence interval that includes 1, indicating no significant difference

between treatment groups.

Now, in an analysis of the same data, but restricted to the psychiatric adverse events with a severity rating of moderate or severe, also showed no difference between varenicline and placebo, with a risk ratio of .90 and a 95 percent confidence interval that included 1. That's on the second line.

An analysis of the psychiatric adverse events was also conducted by psychiatric history of the subject, as shown in the last two lines. While the incidence of psychiatric adverse events was higher in patients with a history of psychiatric disorder, the results show that there was no difference in psychiatric adverse events between varenicline and placebo in subjects either with or without a history of psychiatric disorder, with a risk ratio of approximately 1 in both of these groups.

Now, we also conducted a meta-analysis of these 18 studies using the same composite endpoint of psychiatric adverse events that will be used in

the ongoing neuropsychiatric safety study, study 1123. And the results are shown here for all patients and by history of psychiatric disorder.

The number of events and subject years are shown for both treatment groups and the risk ratios are shown in the column on the right. Consistent with the previous analyses, there was no increased risk of psychiatric adverse events for varenicline in the overall analyses. In addition, there was no evidence of increased risk of psychiatric adverse events with varenicline in either patients with or without history of psychiatric disorder.

The best information we have available to approximate the study, study 1123, is the 18-study meta-analysis. And as mentioned earlier, we know that the blinded rate for the composite endpoint in study 1123, at the second interim analysis, was 4.5 percent.

Now, this blinded study is randomized equally across treatments and has planned to enrolled equal numbers of patients with and without psychiatric history. Now, in our own existing

18-study analysis, if it was distributed in the same way, the projected overall rate of the composite endpoint for the 18 studies is 4.2 percent, which is very similar to that found in the interim analysis for study 1123 at the second interim analysis.

Results from the meta-analysis of 18 studies has recently been added to the Chantix label and includes the information that's on this slide. The label states that 5,072 Chantix patients were included in the analysis and that some had psychiatric conditions. And it goes on to state that the results showed a similar incidence of common psychiatric adverse events in patients treated with Chantix compared to patients treated with placebo.

A meta-analysis of five studies that included the Columbia Suicide Severity Rating Scale, as I mentioned earlier, was conducted to assess the effects of varenicline on suicidal ideation and behavior. A five-study cohort that included 1130 subjects treated with varenicline,

777 subjects treated with placebo, and included two studies with patients with psychiatric disorder was conducted. The outcome measure was responses for suicidal ideation and/or suicidal behavior as reported on the Columbia Suicide Severity Rating Scale.

Results from this meta-analysis are shown here. On the left-hand side, the number of events, the number of subject years, and the incidence rate per 100 subject-years is shown for varenicline and placebo.

On the right is the forest plot of the risk ratio with the 95 percent confidence interval. And as shown on the bottom line, the estimate of the risk ratio for varenicline versus placebo during treatment was .79, and the 95 percent confidence interval included 1, showing that there was no increased of suicidal ideation or behavior with varenicline.

Now, the findings from this meta-analysis have also been included in the recently-updated Chantix label. As I have highlighted here, the

label states that the results show no increase in the incidence of suicidal ideation and/or behavior in patients treated with Chantix compared to patients treated with placebo, with a risk ratio of 0.79, as shown on table 1, which I'll show on the next slide.

The label also notes that 48 of the 55 patients who reported suicidal ideation or behavior were from the schizophrenia and depression trials. And here is the table that I referred to a moment ago. So this is the information that's currently added to the Chantix label.

Now, as we mentioned, the boxed warning states that there are changes in behavior, hostility, agitation, depressed mood, and suicide-related events, as well as worsening of pre-existing psychiatric illness have been reported in patients taking Chantix.

Now, results from the meta-analysis of 18 studies as well as the meta-analysis of suicidal ideation and behavior in five studies, these results are now included in the Chantix label,

which validates the importance of this information in characterizing the safety profile of varenicline.

So based on the results from the clinical studies as well as the meta-analyses, we can conclude the following, that there's no evidence of worsening of pre-existing psychiatric illness with varenicline, as measured by psychiatric scales in subjects with schizophrenia or schizoaffective disorder or major depressive disorder; that there's no evidence of an increased risk of psychiatric adverse events with varenicline other than sleep disorders, as shown in the meta-analysis of 18 placebo-controlled studies.

There's no evidence of increased risk of psychiatric adverse events with varenicline in patients with or without a history of psychiatric disorder, as shown in the meta-analysis of 18 studies. And there's no evidence of an increased risk of suicidal ideation or behavior using the Columbia Suicide Severity Rating Scale with varenicline versus placebo.

So in sum, the data from placebo-controlled studies do not support an increased risk of neuropsychiatric events in Chantix-treated patients. Thank you.

I'd now like to introduce Dr. Robert West, who will review the results from large observational studies. Thank you.

Industry Presentation - Robert West

DR. WEST: Thank you. Good morning. My name is Robert West, and I am director of tobacco research at University College London. I've been researching smoking cessation for more than 30 years, and I undertake a wide range of studies in the area, including clinical trials, large population surveys and cohort studies, and analysis of clinical data. And in my work, I've been addressing many of the issues that come up in interpreting evidence in large observational data sets.

Thank you very much for allowing me the opportunity to present the independent observational study data here. My declaration of

competing interests is shown on this slide. I am receiving a fee for doing this, but obviously the fee will be going to my research program.

In pursuit of the aim of establishing whether neuropsychiatric adverse events occurring in people who are using or who have recently used Chantix probably reflects a causal association or probably does not, you've heard that clinical trial data shows similar, serious neuropsychiatric event rates in Chantix and placebo conditions.

To complement these studies, a number of independent investigators have used large observational data sets to compare the neuropsychiatric adverse event rate in smokers using Chantix compared with nicotine replacement therapy, which can be presumed to carry no excess risk for these people, and bupropion, where no increased risk has been demonstrated, but where one is suspected.

Five major studies of this kind have been published. These studies were conducted in a broad selection of populations from U.K. primary care

patients, the entire population of Denmark, the U.S. Military Health System, which includes active duty and retired military and their dependents, and the USVA, which includes U.S. veterans, and eligible family members, and survivors.

The second study of primary care patients in the U.K. is an extension of the earlier one involving more cases and additional statistical analysis, so I am not going to consider the earlier one here. The Danish study compares varenicline with bupropion, which is suspected might cause neuropsychiatric adverse events. And in the case of the VA study in the U.S., we only have summary information.

Now, the design of the studies is broadly similar. They estimate the rates of occurrence of designated neuropsychiatric events in patients who have received a prescription for Chantix versus one or more comparators, and the choice of comparators is designed to ensure maximum comparability of factors other than medication choice.

These population-based observational studies

had large sample sizes, including approximately 10,000 to 30,000 patients treated with varenicline and include patients with and without a history of psychiatric disease treated with varenicline in routine clinical practice. The authors of the study recognized that there may be factors influencing the choice of medication that could be related to the risk of neuropsychiatric adverse events.

In particular, it's possible that patients prescribed varenicline would have a lower pre-existing risk of neuropsychiatric adverse events. And this could happen if, for example, clinicians were reluctant to prescribe varenicline to smokers who had a history of psychiatric disease. Therefore, the studies needed to assess the extent of such possible bias and to adjust for it statistically.

I'm going to focus on the two studies comparing varenicline with NRT for which detailed information is available. Then I'm going to begin with the Clinical Practice Research Database, or

CPRD, study in the U.K., which is conducted by Kyla Thomas and colleagues.

This is the largest and involves the most thorough test of the hypothesis by virtue of a range of sensitivity analyses and the most powerful tests of causal associations possible with observational data, that is to say, propensity score matching and use of what are known as instrumental variables.

Propensity score matching can provide better statistical control over potential confounders than multiple regression methods by matching people in each of the groups on a range of variables that could affect the outcome.

Use of an instrumental variable is potentially even more efficient if one can identify a variable that has a strong association with the risk factor, in this case, the use of varenicline versus NRT, and no conceivable association with the outcome except through that exposure variable. If it turns out that it has an observed association with the outcome, then this provides evidence that

the association between the exposure variable and the outcome is causal.

The CPRD study used the disposition of the prescribing GP and not the particular choices around his patient, this particular patient, to describe varenicline versus another smoking cessation medication as the instrumental variable using each of the last seven prescriptions.

Now, it turns out that this had a very strong association with the individual case prescription, but I would argue and the authors argue that there's no plausible direct impact on suicide and self-harm for that instrumental variable in that particular patient. And in fact, they demonstrate minimal associations with relevant confounding variables.

This form of analysis has quite an extensive history in pharmacoepidemiology since its introduction by Alan Brookhart in 2007. This slide shows more details about the methods, and the study was published in the British Medical Journal, and the conclusions were clear. The authors

concluded -- and I quote -- "There is no evidence of an increased risk in suicidal behavior in patients prescribed varenicline or bupropion compared with those prescribed nicotine replacement therapy. These findings should be reassuring for users of smoking cessation medications."

When interpreting their findings, it's important to note that the authors went to considerable lengths to address the issue of possible confounding. With the instrumental variable analysis, they reported that the instrumental variable had shown itself to be strongly related to group assignment, that is to say, varenicline versus NRT, but there was no evidence of an association with suicide and self-harm.

Moreover, when they did a statistical test as to whether the imputed risk difference associated between varenicline, and suicide, and self-harm through the instrumental variable was different from the conventional regression model assessing risk difference in this case, they found

no evidence for such a difference.

So while the standard regression found a very slightly reduced rate for varenicline versus NRT, and the instrumental variable analysis showed a very slightly increased rate, this represented a marginal shift which was well within the error variance.

The authors also very clearly tested carefully the association between instrumental variable, an index made from the seven prior prescriptions, and possible confounding variables, and found that while there was a very small increase, small association for alcohol misuse, this was marginal compared with the association with the index prescription.

In view of this, while it's just about conceivable that there may have been residual confounding with unmeasured variables, the authors of the study have told me -- and I agree with them -- that this must be considered exceptionally unlikely.

Now, I've been in correspondence with the

study statistician, and he makes what I think is a very telling point. And if I may, I'll quote, "Also note that in the instrumental variable analysis, we found no evidence that varenicline increased the likelihood of suicidal self-harm. This means that if there is a confounder of the instrument outcome association, it would need to be a precise size to offset the hypothesized adverse effects of varenicline.

"If the effect of the confounders were even slightly too big, we would have found a protective effect of varenicline, so I do not find it plausible that residual confounding could explain why we didn't find an effect in our instrumental variable results."

He also comments, "A reduced likelihood of sicker patients being prescribed varenicline would not affect our instrumental variable results. As long as the patients' comorbidities were not associated with their GP's preferences, the IV results should be unbiased." He goes on to say, "If sicker patients were less likely to visit GPs

who frequently prescribe varenicline, our instrumental variable results could be biased downwards, but we found little avoidance of this."

Again, as with confounding, the selection effect would have to be a very specific size to offset the hypothesized adverse effect.

The authors also looked at a subsample of those who had been prescribed varenicline for the first time, reducing the risk of bias from inclusion of patients who had shown themselves to be tolerant to varenicline's side effects and the results were identical.

The authors went further and examined a range of follow-up points. And they found no evidence at any follow-up point or any difference between them. Thus, the parameters were similar, whether one looked at the time period when patients were taking the medication and long after they'd stopped taking it.

It's also important to note that the authors examined whether there was any suggestion of an interaction with a previous psychiatric history and

they found none. And they looked for an interaction with time before versus after the media publicity, which began in 2008, to assess whether any channeling of sicker patients away from varenicline following the media reports and label changes might have led to confounding, and they found no evidence for one.

So in my view, the CPRD study was the most thorough and rigorous examination of the hypothesis that varenicline causes an increase in suicide and self-harm rates that is possible to conduct in an observational study. Not only did the study not find a statistically significant increase, it actually found no hint of an increase in risk.

There was some comment in the British Medical Journal following the Thomas study that even with propensity score matching, there remained an apparent benefit of varenicline on all-cause mortality, which was showing residual confounding.

But it's essential to keep in mind that, even if this were the case, this was for mortality and not for neuropsychiatric events. These are

quite separate and unrelated outcomes. And so in my opinion, to infer that there is residual confounding for neuropsychiatric events wouldn't be correct. In any case, the instrumental variable analysis supported a lack of association between varenicline and these neuropsychiatric outcomes and addressed the issue of residual confounding by unmeasured factors.

So the conclusion from the Thomas study, I think, must be as the authors state and was accepted by the BMJ's peer-review process, which is that it showed no evidence for an association between varenicline use and suicide and self-harm or indeed, although I have not discussed this, the endpoint of initiation of treatment for depression.

If we now turn to the Military Health System study, or the Meyer study, this was also a very well-conducted study that made excellent use of the data available. It used routinely-collected data to establish whether receipt of a prescription for varenicline was associated with hospital admission for a neuropsychiatric event. And it, too, used

propensity score matching, and the observed hazard ratio was found to be close to 1.

A potential limitation is that the outcome measure was not corroborated with patient notes, but I think it's very difficult to see how this could have created a bias that would actually alter the hazard ratio.

With the other two studies, we see the same pattern of results, and in fact the pattern of findings is exactly what one would expect from a random variable that had no association with serious neuropsychiatric adverse events.

I have to stress this. In multiple studies, using a variety of methods and populations with various outcome measures that have looked in every possible way to see whether an association can be found between varenicline use and serious neuropsychiatric events and to address issues of possible confounding, no such association can be found. To argue, then, that such data in some way to be discounted relative to spontaneous, uncorroborated reports of incidence doesn't seem to

me to be reasonable.

There does remain the question as to whether, even with these very large samples, there is sufficient statistical power to detect the size of effects suggested by the spontaneously reported cases in the postmarketing database.

But note that, by detect here, we're talking about achieving a 95 percent confidence, a near certainty that there is an effect of varenicline. And it also has to be -- it's also been suggested that even with the very large samples involved, there remains a remote possibility that varenicline does have a small effect. And that may be true and goes to the issue of whether it's appropriate to include a warning.

However, as I understand it, that's not really what the boxed warning is taken to mean. The boxed warning is taken to me that it's probable that there's a causal association between varenicline use and serious neuropsychiatric events. And to test this hypothesis, we need a slightly different approach.

To assess this directly, we can calculate what are known as Bayes factors, also known as likelihood ratios, to see whether the data supports the hypothesis of a difference of, let's say, up to a 50 percent increase in hazard ratio, more than they support the hypothesis of no difference.

Bayes factors are now widely used for hypothesis testing because they capture the key parameter in which one is interested with a single number that takes account of effect size and statistical power. The Bayesian analysis lays out what is essentially the same information as I have shown you, but in a way that more clearly addresses the issue of interest.

So a Bayes factor of more than 1 favors the hypothesis of at least some increase. In this case, I'm going to test the increase of between naught and 50 percent in serious neuropsychiatric events, given the data, while a Bayes factor of less than 1 favors the hypothesis of no increase.

So with the help of my statistician colleagues, I have tested the hypothesis of no

increase in risk -- sorry, no difference in the serious neuropsychiatric event rate compared with nicotine replacement therapy and the hypothesis that there's a difference of somewhere between naught and 50 percent increase in risk, with no reason to favor any figure in between, i.e., what's known as a uniform distribution.

The results in general, as you can see from this slide, favor the hypothesis of no increase. Now, I have tested a range of different alternative hypotheses, naught to 50 percent, non-uniform distributions, and the results remain essentially the same.

Note that even with the Military Health System study, where the point estimate was actually slightly higher for varenicline, it's still, if anything, slightly more likely that there's no increase in risk, and there's an increase of up to 50 percent. And the reason for that is that the increase found was so close to zero.

So to sum up the findings from the observational data, they tell me that while we

could obviously never completely rule out the possibility that varenicline is associated with an increase in neuropsychiatric events, the data point more strongly towards there being no increase than to even a small increase, which I have defined as up to 50 percent on a very low baseline rate.

I think it's worth saying that I have shared these conclusions with a number of colleagues, including Dr. Thomas and Dr. Neil Davies, the statistician involved in her study, and they concur with this conclusion. The studies all have limitations, but they address the issue from different angles and different populations, and they also have some considerable strengths.

One can always argue that the outcome measures used in the observational studies are somehow not the right ones or that they lack precision, but when it comes to serious neuropsychiatric events and deaths associated with these, I think such an argument is hard to sustain, given the multiple data sources that have been used.

So in my view and that of colleagues with whom I have discussed this, and clearly the view of the reviewers and the editors of the journals in which the findings have been published, the observational data are highly relevant to the issue we're considering here. And as I understand it, the boxed warning is intended to mean that varenicline probably increases the risk of neuropsychiatric events, but the observational data are telling us that it probably doesn't.

Now, I'd like to turn finally to my perception of the public health considerations and why I think removing the box so that the label more accurately reflects the state of evidence is actually a matter of urgency.

Everyone in this room will be aware how important it is for smokers to stop in order to protect their health. However, it's one thing to know this and it's another to be aware of all the implications. Evidence from longitudinal studies makes it clear how urgent it is for smokers to stop because once they reach their mid-30s, it's no

exaggeration to say that the evidence tells us that for every day of continued smoking, smokers of the kind that we're dealing with here lose an average of six hours of life expectancy. Every month loses a week and every year loses three months.

In the next six months, I estimate, that on the basis of the CDC statistics, that some 8 million U.S. smokers will try to quit. And there can be no doubt that many if not most of these would have their chances of success dramatically improved if they were to use this drug, varenicline, rather than trying to go cold turkey or indeed using other available medicines.

If even a tiny proportion of these are put off using or denied access to varenicline because they or their clinician has misinterpreted the evidence on neuropsychiatric side effects, there will be literally thousands of personal tragedies that could have been avoided.

We rightly regard every single human life as precious. Avoidable deaths resulting from errors in public health are just as important in those

resulting from clinical mishaps. Just because we don't know who the individuals concerned are, obviously, doesn't mean that they're avoidable deaths or any of the less tragic.

In public health, every decision has to be judged in terms of the costs and benefits. And in my view, the cost of delaying the kind of label change being requested would be considerable. I appreciate the dilemma faced by the FDA, given the lack of precedent, but to leave a misleading boxed warning in the label is not, in my view, the safe option. It's the risky option. Thank you very much for your attention.

DR. WOHLBERG: Thank you, Dr. West.

As we have been showing you, the findings from these observational studies were also included in the recently updated Chantix label. Interpretive statements regarding the result are highlighted in yellow on the next slide.

Although limitations of these studies are clearly described, the current text highlights the lack of increased risk compared to NRT in the MHS

and the VA studies, compared to bupropion in the Pasternak study of emergency department visits or in-patient admissions, and compared to NRT for the risk of fatal and non-fatal self-harm in the Thomas CPRD study.

We agree with the division that postmarketing reports regarding serious neuropsychiatric events constituted a safety signal in 2007 and 2008. However, the aggregate data, now available from 18 randomized clinical trials in 4 independently conducted observational studies, do not appear to validate that concern.

To reiterate, the current control data consistently show no evidence of an increased risk of serious neuropsychiatric events when compared to placebo, bupropion, or NRT.

There is no evidence of increased risk of psychiatric adverse events with varenicline versus placebo in subjects with schizophrenia, or schizoaffective disorder, or major depressive disorder;

No evidence of increased risk of psychiatric

adverse events with varenicline versus placebo in a meta-analysis of 18 placebo-controlled studies;

No evidence of increased risk of suicidal ideation or have with varenicline versus placebo in a meta-analysis of five studies using the Columbia Suicide Severity Rating Scale;

No evidence of increased risk of self-harm with varenicline versus NRT and observational studies; and no evidence of increased risk of hospitalization for psychiatric diagnoses with varenicline versus NRT or bupropion in these observational studies.

Again, while each source of data has its strengths and limitations, the control data suggests that there is no increased risk of serious neuropsychiatric events in patients treated with varenicline compared to patients treated with these comparators. These conclusions are especially robust given the hierarchy of evidence and the convergence of results between clinical trials and the observational studies.

That brings us to the question of how to

fairly and accurately label Chantix. When warning about the risk of serious neuropsychiatric events will remain in the label, the key issue for this committee to decide is whether the risk of serious neuropsychiatric events shall remain as a boxed warning.

Put another way, you are essentially being asked to give an opinion on whether the evidence supports a causal association between varenicline and serious neuropsychiatric events and thus the inclusion of the most stringent and highest level of warning available to the FDA.

Within the clinical trials and observational studies presented today, the rates of serious neuropsychiatric events in patients taking varenicline are similar to NRT, yet Chantix has a black-boxed warning, while NRT is sold over the counter.

We agree that patients quitting smoking should be monitored. However, continued inclusion in a boxed warning sends a message that is not supported by contemporary data. That message can

lead to fewer smokers achieving the important health benefits of smoking cessation. Allow me again to quote Dr. Evins, "It's time to unring the alarm bell on varenicline." Thank you.

Clarifying Questions to Industry

DR. PARKER: We'll have five minutes for clarifying questions. I'm going to give you that as a forewarning. And I am saying that because I know at least one person who wants to get up, and move, and maybe go somewhere. So let me ask the committee if there are clarifying question. I'm going to ask that you raise your hand, and also place your card on its side, and be certain that Ms. Bhatt gets your name on the queue.

Remember to state your name for the record before you speak, and please direct your questions to a specific presenter, and keep them brief and focused if you're at all able to. Thank you very much. And we first have Dr. Morrato. Thank you.

DR. MORRATO: Thank you. This is Elaine Morrato. Thank you for the presentation. I had just two quick questions to clarify case

ascertainment as it relates to assessing causality as well as the strength or quality of the evidence that you've provided.

So the first question relates to the case reports. In reading the briefing material, I was really struck by findings related to dechallenge and rechallenge evidence, that there was a consistent time to serious neuropsychiatric onset and that the studies that the FDA have done have been outside the window of the stimulating reporting. So that suggests to me these are not random adverse events. And I am wondering -- you did not touch on the case report findings from that standpoint.

Do you have comment?

DR. WOHLBERG: Thank you very much. This is an important question and one that comes up all the time. For consistency in everybody's understanding, let me define dechallenge and rechallenge so that we can frame this.

A positive dechallenge would be cessation or reduction in symptoms in the absence of other

therapeutic measures after discontinuing a drug. A rechallenge or positive rechallenge would be reemergence of those symptoms with re-introduction of the drug and no other therapeutic measure.

So when we look at the cases in which we have information about dechallenge and rechallenge, which is a very small percentage of cases, unfortunately, we do see cases of positive rechallenge.

Typically, what we see, though, is that in at least as many and sometimes twice as many cases, the information is available where the rechallenge is negative. And when we actually look at these cases and look at the case details, sometimes the information is not quite consistent with the observation of a positive rechallenge. So while we do see it, oftentimes, we do not.

The other thing to remember is that if we were talking about a blood pressure medication where you can objectively measure the blood pressure and the changes that are observed with discontinuation and reintroduction of the drug,

there's an objective measure.

But in the case of varenicline, we are treating patients for smoking cessation in a population where we've shown you the occurrence of these events in the population and the occurrence of events with withdrawal, so that these are episodic and may actually represent reemergence of those symptoms.

Maybe to give you a little bit more information about how that may have clinical implications, let me have Dr. Evins provide some perspective on that.

DR. EVINS: Thank you. Good morning. My name is Eden Evins. I'm a psychiatrist at Mass General Hospital in Harvard Medical School. And I direct the MGH Center for Addiction Medicine, and I am a member of the schizophrenia clinical and research program. I have worked for nearly 20 years to test safety and efficacy of smoking cessation treatments in those with or without psychiatric illness and treatments for schizophrenia, particularly negative symptoms and

cognitive dysfunction.

This is a great question, and in a number of cases, we see positive rechallenge. And when we look closely, it becomes quite understandable. In one of the cases in the Pfizer database, I found a case in which citalopram, the person's antidepressant medication, was discontinued concurrently with both challenges of varenicline. And while this seems to be questionable clinical practice, I'm told this happens all the time.

What we see clinically much more commonly is people will go on varenicline. They'll have success. They'll quit smoking. They'll experience nicotine withdrawal symptoms, particularly people with a high severity of dependence. And they'll have irritability, or anxiety, or symptoms that feel intolerable.

They'll stop the varenicline because they may have misattributed that to varenicline treatment. They'll resume smoking. The AE resolves, and we might be able to convince them to try it again. They try varenicline again. They

quit, and they have nicotine withdrawal symptoms. And so here you have a positive rechallenge.

In a particular case, in a patient who is a high-functioning VIP patient, actually, at our hospital, she presented to me wanting to quit smoking. She had two previous trials of varenicline only lasting a couple of days because she felt intolerable anxiety, irritability, and felt she couldn't tolerate it. So she wanted to try something else.

I tried NRT and bupropion. These didn't help her quit smoking. And so at that point, I sat down with her and actually showed her the data, showed her the AE events with varenicline, but also the high AE events with placebo, and let her know I would follow her carefully, and I think changed her expectations somewhat, such that she tolerated a trial of varenicline and she quit smoking. And she stayed on for about six months, and she's still quit today.

To me, that really illustrates this expectation bias. So she had a positive

rechallenge on two occasions, but then with some education and change in her expectations from what she had heard from the media and understood from the black-boxed warning, she tolerated the medication.

I hope that's helpful.

DR. MORRATO: Yes.

DR. PARKER: So it's 10:00, and unfortunately, we've got several people who have clarifying questions they'd like to pose, but we are at our break time. So what I'm going to do -- we've got the names on the list. I'm going to ask Dr. Emerson to state his question, and let's answer that. And then we'll move to the break, and we'll convene after that. We have your names in the queue. I'm sorry that the time has run short for this.

Dr. Emerson, thank you.

DR. EMERSON: So these are really just two very short questions. The first is related to slide M-94, where you regarded that it was inconsistent with the FDA guidance regarding a

boxed warning, yet you only listed the first of the three reasons that the FDA stated. Is it Pfizer's opinion that only the first obtains for a boxed warning?

Then my second question is just a quick one for Dr. West. He spoke so fervently in favor of the observational data, I just wanted to make certain that he felt that that would outweigh any results that we had in the clinical trial that's currently ongoing.

DR. WOHLBERG: Maybe we'll have Dr. West answer the second part of the question first.

DR. WEST: Thank you. Yes. Well, I think the thing about this is we're building a picture. It's like building a jigsaw. And you take the observational data on its own. That tells you one story because it addresses limitations of the clinical trial data. The clinical trial data clearly address limitations of the observational data.

I mean, it's probably easier for me to say this than for Pfizer to say this, but I think that

when you look at the numbers involved and you look at the history, not only of the observational data, but also the clinical trial that's been accumulated, it just seems highly -- and you look at the event rates that we already know what they are with the interim analysis, with the study, it seems highly improbable to me that there would be a change in the overall picture.

But I wouldn't want to say that the observational data trump anything. I don't think any type of data trumps any other data. I think we're building a picture. But what's really remarkable to me is how consistent that picture is with the highest quality data available, where you actually have a comparator.

So dose that answer your question?

DR. WOHLBERG: I think that's really what we've been saying, that the convergence of the results leads to the greatest strength of the results from the trials and the observational studies.

As far as the first question that you

raised, can I see M-14 shown? The conclusions obviously were summarizing, but these are the three typical uses. The FDA also described two other scenarios. The third instance on this slide applies to restricted distribution, which is not applicable to the Chantix scenario.

So we have the first two options, and in the second case, remember that the guidance, which is a guidance, does have some overlap between the boxed warning and the warnings and precautions section.

So if I can have M-15? There is the ability in warnings and precautions to describe other potential safety hazards that are serious or otherwise clinically significant because they have implications for prescribing decisions or patient management. Part of that patient management can include monitoring.

So there is an overlap. The question is, how severe is the risk to warrant labeling in warnings and precautions versus a boxed warning? And what we've said today is that we think that the available evidence is inconsistent with a boxed

warning, based on the data that we have right now. And that data is convergent between clinical trials and observational studies.

DR. PARKER: So I spoke incorrectly. Our break actually starts at 10:10, so we've got a couple others in the queue. Let me call on them. My apologies for that. Dr. Marder?

DR. MARDER: Yes. I had a question for Dr. West about how representative the private-practice patients are when it comes to people with serious mental illness. I mean, they're seen in primary practice. Are we able to see the risk in people with more severe, unstable illnesses?

DR. WOHLBERG: I'll have Dr. West comment, but then I'd also like to have Dr. Prochaska maybe provide some additional insights. Dr. West?

DR. WEST: As you probably know, in the British system, with the National Health Service, essentially, the general practitioners are the gatekeepers. They basically treat everybody and then send people off to specialists.

What's very remarkable about the data coming from the Thomas study is -- well, I guess it's not remarkable, but it looks very representative of the general population of patients that they see. If you look at the history, for example, of treatment for depression, history of other psychiatric diagnoses in that population, then the rates are high. It's in the region of 40 percent or so, for example, for depression.

So I think it would be reasonable to say that, in terms of their psychiatric history, they are highly representative. The CPRD database, as you may know, it's a very well-respected database precisely because it does capture so well the kind of sample of the national population.

DR. WOHLBERG: Perhaps the reason for having Dr. Prochaska elaborate a little bit is because she does do studies in patients with pretty significant mental illness, so I'd like to hear her comments.

DR. PROCHASKA: Thank you. I'm Dr. Judith Prochaska from Stanford University in the Department of Medicine and was asked to disclose

any conflicts of interest. I am a principal investigator on an investigator-initiated research award from Pfizer. And that was mentioned by Dr. Wohlberg earlier with the non-psychiatric hospitalized smokers.

The question was about how representative the observational data are relative to smokers that are out there in practice. I can speak -- one of the reasons that I'm here today is because I do extensive research with smokers with serious mental illness, recruited from the hospital setting. And we do, as you saw, see a number of serious adverse events that occur when people are going through the process of quitting smoking, but also more so just that process of dealing and struggling with a chronic mental illness.

In terms of the observational data, as you heard from Dr. West, it does have -- included people with mental illness, but also really importantly, the clinical trial data that have come to light since the time that the boxed warning was put on, that varenicline now has been studied in

individuals with clinical depression; that it has been studied now in multiple trials with individuals with schizophrenia, showing both efficacy as well as no signal for serious adverse events.

DR. WOHLBERG: Maybe very quickly, Dr. Evins, as a treating psychiatrist, you can probably address the clinical aspects of this.

DR. EVINS: Dr. Evins from Mass General Hospital. And Steve, I share your concern that big observational studies often may include people with some psychiatric illness, but not many with severe mental illness. I agree with you.

But what's come to light is trials by Hong, Shim, Weiner, Evins, and in addition to the Williams trial in schizophrenia, placebo-controlled trial, which show actually improvement in cognitive function in some of the endophenotypes associated with schizophrenia, but a very clean safety profile in terms of PANS scores, BPRS scores, as well as spontaneously reported adverse events. There's also recently the Chengappa trial in treated

bipolar patients.

So we are gathering a database. And there was recently, actually just this month, a meta-analysis of the schizophrenia trials showing no increase in discontinuation from AEs, for all-cause, and only an increase in sleep disorder and nausea, but no increase in depression, irritability, the neuropsychiatric adverse events that we are concerned about here.

DR. PARKER: Dr. Gerhard?

DR. GERHARD: My question is for Dr. West. And I apologize that I can't speak and look at you at the same time. Regarding the observational studies, one of the main concerns obviously is that the types of events that we are talking about here are very likely to be incompletely captured in both claims and medical record data.

Could you speak for a moment to the direction of the bias that that would induce and to what extent some of these sensitivity analyses or some of the methodological approaches that you talked about, whether they would address these

concerns?

DR. WOHLBERG: The events that were captured are spontaneously reported events. And these are the events that were seen by the patients both in the observational studies as well as in the clinical trials. Some of the studies utilized a Minnesota Nicotine Withdrawal Scale to capture symptoms. Some of them use the Columbia scale, as you've seen, to capture events of suicidality. And then others use what's called a neuropsychiatric adverse event inventory to prompt for those events, sir.

DR. GERHARD: Just to clarify, I was talking about the observational studies, not the spontaneous reports or the trials, just specifically the observational data.

DR. WOHLBERG: Right.

Dr. West, do you have some thoughts on that?

DR. WEST: I think that's right in principle. I think, when you come to the more severe end of the spectrum, I think that's likely to be less of an issue. If you look at the kinds

of events that are actually covered -- obviously, the Thomas study covered suicide and self-harm, hospitalization for self-harm. These are serious but limited. I didn't talk about it, but also, they looked at treatment for depression as well and clearly didn't find an adverse signal there.

The Military Health System study had quite a wide range of events, and that was for hospitalization. And as you may know, or people in this room may know, there was an additional analysis that was done looking at outpatients and found basically, essentially the same issue.

So I think the idea that in some way we're really not capturing the full spectrum of the severe end of the adverse events that we could do is probably unlikely. But even if that were the case, I think the question is, can we come up with a plausible way in which that would differentially affect the groups that are being compared. And I'm not sure that I can.

One probably can come up with something, but it would be struggling, I think. So I think it's

really the differential effect that's the key here. And actually, when you look at the rates and things like suicides, the ones that are appearing in the studies are very similar to the rates that you observed in national samples as well.

So I think, again, it speaks to the issue that it probably is capturing pretty much what we are looking for. And bear in mind that it's not that the difference between the conditions here is like there but not significant. We're just not seeing it at all. So it would have to be a pretty big bias to overcome that.

DR. WOHLBERG: Perhaps one other point is that, while in the primary endpoint for the Thomas study, we're looking primarily at depression, in the hospitalization composite endpoint from that study, agitation and hostility were symptoms that were associated with some of the personality disorders, and that was captured.

So we're seeing what was reported. And the Meyers study is another example. We're seeing the discharge summaries from patients with whatever

they were discharged with.

DR. PARKER: So I'm going to insert one follow-up question to Dr. Emerson. So as I understand it, the request is to remove the black boxed warning. And we have a prototype of what that would look like in the briefing documents. In case you didn't get to almost page 400, it's down in there in our briefing documents. And it shows what it would actually look like in a track-change mode.

So what I wanted to understand, based on the current observational and clinical trial data, the request is that that be taken out of a black box and some of that content moved to another section. My question is, once the results of the RCT are available and analyzed in 2015, would it go back in if that analysis were to be compelling?

I just want to understand where that sits because, again, that gets back to the question about weighing the results of data.

DR. WOHLBERG: It's the question that comes up time and time again, why would we do this, and

would you put the box back in. Yes. The answer is yes, if the data supported that. What we believe is that the label should most accurately reflect the current data. The current label with a boxed warning, in our opinion, does not accurately reflect the overall risk of the product.

We agree that there should be monitoring. Show FT-13, please. Again, this is from the FDA briefing document. We don't think that these data warrant a boxed warning. We agree that patients who quit smoking have emergence of neuropsychiatric events, but causality is still out. The jury is still out on that. And until we have a clear answer that suggests or concludes that there is a risk, we shouldn't have a boxed warning.

DR. PARKER: At this point, we're going to take a break. We'll take a break, and we'll reconvene at -- we'll take a 15-minute break, and we will reconvene at 10:30, at which time we will begin the FDA presentations.

We still have a couple folks on the queue. I've got those names. And if we have time later,

we'll come back to those clarifying questions. Thank you for your time.

(Whereupon, a recess was taken.)

DR. PARKER: So let me just let folks know that we continue to have a queue here for some clarifying questions. And I'm going to ask Dr. Pickar, Dr. Morrato, Dr. Roumie to hold on to your questions. And we will hopefully be able to come back and work those in later, but we're going to move forward so that we can try to keep on schedule.

I would like to ask the sponsor perhaps over the lunch break, we do have in our background documents the proposed label changes and what they look like in track changes. If you don't mind, if you could get us a couple copies of those that we can circulate around the table for people who don't have access to them electronically. I think it's helpful to see exactly what they would look like, not the ones that have already been agreed upon, but the proposed ones, so that we can actually put our hands on those. We could let those circulate

while we're in discussions this afternoon.

So we'll now continue with the FDA presentations. Thank you.

FDA Presentation - Celia Winchell

DR. WINCHELL: Good morning. My name is Celia Winchell. I am the medical team leader for addiction products in the Division of Anesthesia, Analgesia, and Addiction Products here at CDER. And I have just learned that I have been mispronouncing the name of this drug for the last 10 years. So please forgive me. Old habits die hard.

In this presentation, I am going to take you back in time to how we wound up writing the label the way it is today. My remarks will be qualitative only and not quantitative, but I am going to try to trace for you what led us to believe that there was an issue with Chantix.

Let's see. First to walk you through the timeline, as you know, Chantix was approved in May of 2006. In the following summer, as you've heard, we heard from colleagues in the European regulatory

agency that they were looking into a signal for suicide seen in their postmarketing pharmacovigilance data.

Then while we were preparing an information request to Pfizer to ask for more information on this topic, a highly publicized incident occurred, which we've come to call the Carter Albrecht case, involving an episode of bizarre behavior that some people attributed to Chantix. Consequently, we broadened our information request to include both events involving suicidal behavior and events involving aggressive and irrational behavior.

This slide shows you what we asked for in that request. We asked for events coded to the MedDRA terms that were in the standardized MedDRA query for suicide and self-injury. That wasn't difficult; additional information, anything we could have about the Albrecht case; and case reports involving adverse events coded to MedDRA terms.

We gave a list of ones we could think of at various levels of the hierarchy and asked Pfizer to

come up with others as well to try to capture this other type of event, where somebody behaved very unusually in the context of using Chantix and to provide us with a summary and analysis of the cases.

Then we received the response. It came in several parts over a period of time, and the submission included 102 suicide-related cases that had been reported to Pfizer from launch through May of '07. And most of these reports were not yet in our own database. We also had 525 case reports, based on the search for aggressive and irrational behavior, which included 119 reports of aggressive behavior, 33 of which involved physical aggression.

Pfizer's theory was that the symptoms were explained by smoking cessation itself, unrelated to drug use, and that was a lot of people's theory and maybe even my theory at first. But as I read through the description of the cases, I was struck by several narratives that made a compelling case for drug-relatedness based on timing and other features that I'll go through.

Many of the cases that were submitted featured hallmarks of drug-related events, such as the onset of the events, frequently being shortly after the patient started taking Chantix or when the patient titrated up to the full dose. You probably know that the treatment regimen for Chantix begins with a half-milligram once a day, titrates up after a few days to a half-milligram twice a day, and then finally at the end of the week to 1 milligram twice a day. And the patient sets a quit day that's supposed to fall at the end of two weeks of treatment.

There are also examples of dechallenge, in which the symptom went away when the drug was discontinued, as we discussed previously, and rechallenge in which a patient whose symptoms had resolved, re-started Chantix, and had the symptoms occur.

So as I said, initially, there was the thought that these events could just be caused by quitting smoking. Some of the symptoms like irritability and depressed mood are symptoms that

are associated with nicotine withdrawal. But in many cases, the patients hadn't stopped smoking, so nicotine withdrawal seemed less likely.

Additionally, just a theoretical possibility -- this is just speculation at the time -- because Chantix is a partial agonist, it could cause withdrawal by displacing nicotine, which is a full agonist, at the receptor. We know from the situation with opioids that when you displace an agonist with an antagonist or a partial agonist -- which again is the onset of intense symptoms of withdrawal that are foreshortened in time compared to spontaneous experience of withdrawal. So that was one speculation that would be drug related.

Finally, there were a number of cases in which patients specifically articulated that this was something that had never happened to them before, even during previous attempts to quit smoking. So these patients were familiar with the symptoms of nicotine withdrawal and the experience of quitting smoking, and said that it had never

been like this.

Other unusual features of the cases that were striking is that patients were reporting unusual symptoms. I saw these across different case reports, and I'll run through a few typical cases that illustrate these features. People couldn't get out of bed. They didn't feel like themselves. A number of people said they felt like a zombie. And of course, they thought of suicide, which isn't commonly reported as part of quitting smoking. And all of these cases were reported before the publicity surrounding Chantix.

So here are a few examples. This patient specifically articulated that this was unlike a previous quit attempt. In this, a 36-year-old patient is reported to have experienced a complete personality change, a violent temper going into unnecessary rage, stated, "The brain feels like it's been completely scrambled," and this began around treatment day 14. "The consumer believes this is not due to smoking, as they have given up before and never, ever felt like this."

This case illustrates dechallenge and rechallenge, in which a 61-year-old man reported experiencing suicidal thoughts about one week after beginning treatment with varenicline. He stopped, and then he got better. And then he decided to resume treatment. And as he reached the 1 milligram BID titration step, he became very depressed, was in bed for 16 hours, and felt like a zombie. And his wife described his behavior as aggressive. He discontinued varenicline a second time, and most of his symptoms resolved, although not all of them. And we don't know whether this patient had quit smoking or not.

Here's a case illustrating onset with treatment initiation in a patient who had not quit smoking. This 49-year-old woman reported experiencing suicidal thoughts and trouble thinking and concentrating on day 4 of treatment. She had stopped smoking, and then she went back to smoking. And she was smoking a pack a day.

So our colleagues in OSC then reviewed all the cases in our AERS database, what we now call

the FAERS database, we then called the AERS database. So either of those terms will refer to our adverse event reporting system, which collects spontaneous reports directly from patients and consumers and from healthcare providers, as well as from manufacturers.

So they reviewed the cases in the AERS data and felt that they did suggest an association between varenicline and suicidal events based on these features: positive dechallenge and rechallenge, close temporal relationship between the event and the drug, and occurrence in patients without a psychiatric history.

They had reviewed 153 cases. About half had a documented psychiatric history, and about a quarter had a documented lack of psychiatric history, and we didn't know about the rest of them. The median time to onset was less than two weeks. And actually, we had a significant minority of cases actually occur in the context of discontinuing the drug, which is why that's mentioned also in labeling.

They then went on to review the cases that involve psychiatric events that didn't involve suicide, again finding a temporal association between Chantix and the events, onset within the first week of treatment, positive dechallenge.

In addition, they provided us with reports of data mining, in which they compare the number of reports for a particular drug across the entire database to see whether that drug is overrepresented among cases of that type. Anything over a score of 2 is considered high.

In this case, we had scores approaching 20 for some very unusual events, more like 7 or 8 for most of them, but unusual events like violence, hostility, psychotic disorder, and terms like emotional disorder.

One of the most troubling and compelling features of the case reports is that the cases didn't necessarily involve events that were coded to suicide or self-injury, which is where the story began. And they didn't always involve terms involving aggression or hostility. There were

cases where people described a range of symptoms, including perceptual abnormalities, cognitive difficulties, personality change, and a dramatic impairment in their ability to function.

These are not necessarily captured using existing MedDRA hierarchical groupings, or SMQs, and they also don't correspond to specific diagnoses such as you would use in an observational study that might use ICD-9.

Here are some examples of the terms that are applied when reports of these ill-defined difficulties are received. And you can see they're not all in the psychiatric system organ class. And some of the things that consumers say defy coding. For example, if a consumer reports feeling like a zombie, this is usually coded to feeling abnormal. That's SOC general. If a consumer reports thinking like a zombie, that's coded to thinking abnormal. That's psychiatry. And at least one patient reported walking like a zombie and that was coded to gait, abnormal.

One frequent question is, did you see these

in the clinical trials? Naturally, the first thing I did in 2007 was to go back and look at the raw data, and I found it was difficult to determine whether we'd seen cases like this or not. There were cases, for example, of agitation, but with no further information to determine whether that event was something of a nature that was being reported in the postmarketing cases. It was hard to know.

So the process seems to be that the patient comes in and reports an experience, but the patient's actual words, the patient verbatim report, is not captured in the clinical trial database. It's translated, sometimes literally because these are global studies, into a brief term. It's usually a single word. It might be a couple words by the study staff. And then that term is recorded and, subsequently, that is coded into MedDRA terminology.

Given the ill-defined nature of the symptoms that people report, it's easy to imagine different investigators might choose different terms to capture the same phenomena. MedDRA has 30,000

preferred terms. If you know COSTART, it had 3,000.

So they are very, very specific and I have never understood the difference between tension, nervousness, and anxiety. But they are all different terms. Fortunately, those are all in one grouping, but that's not true of all of these. When you're dealing with a symptom like feeling like a zombie, it's easy to imagine. This could be coded very differently by staff at different sites.

On this slide, I have shown you a frequent report in the postmarketing cases: can't get out of bed, couldn't get out of bed, couldn't go to work, couldn't function. How would you cope with that? Here are some choices. Or people will report a short temper, "My wife said I had a short temper," lots of ways to code that as well.

Just to show you that these reports continue to be received, this graph illustrates in gray the total number of serious adverse event reports over time. They are displayed by the event date as opposed to the reporting date. Sometimes they are

not the same.

You can see that the peak occurred in 2007, but that the events continue to be reported. The red line represents usage. It's the same data that Dr. Racoosin showed earlier. And on the next slide, I'll show you most of these cases include terms in the psychiatric, neurologic, and general system organ classes.

This is the same data. That gray shape is the same. And now it is overlaid with a bar graph showing you the contribution of different SOCs to the total reports. Psychiatric is in blue and nervous is in red. General is in green. Because use is falling, the pattern in the number of reports has to be interpreted with caution, but the contribution of the various SOCs is steady.

Just to illustrate that these continue to be reported, this is an example I got in my inbox just a week or so ago, a 39-year-old woman on treatment day 8 reported experiencing forgetfulness, difficulty in understanding, trouble forming sentences, somnolence, nervousness, psychological

problems, asthenia, daydreaming, dropped a cup of tea off a balcony, and apparently walked inattentively into traffic. This patient had not quit smoking.

So in summary, the clinical presentation of the events encompassed and encompasses a wide spectrum of symptoms. Some of them are relatively easy to describe or to classify, suicide and aggression, but they may be underascertained.

You'll see later that spontaneously reported events related to suicide are outnumbered by events solicited using the Columbia Suicide Rating Scale. And that's the reason that we asked Pfizer to include a tool to solicit neuropsychiatric adverse events in the postmarketing trial. It was also used in the depression trial.

Some of these events are not readily assigned to a particular preferred term or to a higher level group term in MedDRA, and they don't even fall into the psychiatric system organ class. Our clinical trial data doesn't always capture enough of the patient's report to understand the

experience. Diagnostic coding schemes that are used in electronic healthcare databases are not likely to capture these events well because they're not diagnoses.

The postmarketing cases offered us a rich narrative with detail about the patient's experiences. And based on review of those cases, in addition to some well-defined phenomena, there also appears to be a syndrome of debilitating symptoms that interfere with people's ability to function in their daily lives. And that appears to be associated with the use of Chantix.

FDA Presentation - Eugenio Andraca-Carrera

DR. ANDRACA-CARERRA: Good morning. My name is Eugenio Andraca-Carrera, and I am a statistical reviewer in the Office of Biostatistics at CDER. And today, I will present findings from our review of the meta-analysis of neuropsychiatric events in clinical trials for varenicline.

Here is the outline of my presentation. I will talk about the background for the meta-analysis, then I will talk about the

meta-analysis trial database and the subject disposition. I will describe the statistical methods used in all the analyses. And then I will present you the results and conclude with a brief summary. So let's move on to the meta-analysis background.

In April of this year, Pfizer submitted to the agency a report of a meta-analysis to evaluate the safety profile of varenicline with respect to three types of adverse events related to neuropsychiatric safety. These events are suicidal ideation or behavior, aggressive behavior and violence, and overall psychiatric events, excluding the sleeping disorders because it is widely accepted that varenicline is associated with sleeping disorders.

Adverse events in these three categories were collected through different mechanisms. Some of them were actively collected and some of them were collected through routine reports of adverse events in clinical trials, as I will describe in the next few slides.

So the first category of events, suicidal ideation or behavior, was collected through two different mechanisms. The first one was the Columbia Suicide Severity Rating Scale questionnaire or C-SSRS, which was administered in five randomized clinical trials. This instrument was designed at the Columbia University Medical Center to assess suicidality, and it has been validated and used extensively in research and clinical practice.

The second way to assess suicidal ideation or behavior was based on routine reports of adverse events in a set of 18 trials. These adverse events were coded to MedDRA preferred terms in the suicidal self-injury Standardized MedDRA Query or SMQ. And preferred terms in an SMQ are validated by a MedDRA advisory panel. And the preferred terms for this particular SMQ are listed here. They include events ranging from mild to severe.

The second category of events, those related to aggressive behavior and violence, were studied through preferred terms that belong in the

hostility and aggression MedDRA SMQ. This SMQ includes terms such as aggression, anger, hostility, and some others, which are listed here. Again, these events were collected through routine reports of adverse events in the 18 trials.

The overall psychiatric events, excluding sleeping disorders, were assessed through adverse events coded in the psychiatric disorders system organ class, or SOC, in MedDRA. A MedDRA system organ class is a high-level collection of terms, which in this particular case includes adverse events related to anxiety, changes in physical activity, depression, personality disorders, suicidality, and other categories which are listed on this slide. Again, these events were collected through routine reports of adverse events in the 18 trials and ranged in severity from mild to severe.

Finally, the FDA review team conducted analysis on one additional endpoint, which I will refer to as the custom neuropsychiatric endpoint or NPS endpoint. As you have heard earlier today, there is an ongoing trial that is assigned to

evaluate the neuropsychiatric safety of varenicline, and this trial is not included in the meta-analysis and is expected to be completed next year.

The custom endpoint presented here was based on the endpoint of this ongoing trial. So while this SMQ shown in the previous slide include adverse events of all severities, this NPS endpoint includes specific adverse events of interest that meet a minimum threshold of severity. So for example, it includes only severe events of anxiety, also depression, and it includes moderate or severe events of agitation, aggression, delusions, and others which are listed here.

Note that, in the ongoing PMR trial, this endpoint is prespecified and is being actively collected. But in the meta-analysis, the endpoint was constructed based on routine reports of adverse events in the 18 trials.

So having described the endpoints, let me describe the trials including the meta-analysis. As you have heard earlier today, the C-SSRS

instrument was administered in five clinical trials, which are shown on this slide. And I will refer to this set of trials as the five-study cohort.

Two of the trials are highlighted in yellow, which are trials 1072 and 1122, and these are the two trials that have a different inclusion criteria. Trial 1072 enrolled patients with a history of schizophrenia, and trial 1122 enrolled patients with a history of depression. We will see later that these two trials contributed to the majority of the cases of suicidal ideation that were collected in the C-SSRS questionnaire.

The complete set of 18 trials in the meta-analysis is shown on this slide. It includes all placebo-controlled studies of varenicline for smoking cessation completed by the cutoff date of September 1st, 2013. It includes the trials in the five-study cohort plus 13 additional trials.

There were a total of 5,072 patients randomized to varenicline and 2,449 patients randomized to placebo. Most of the 18 trials had

an on-treatment duration of 12 weeks, except for trial 1002, which was shorter, at 6 weeks, and trial 1037, which had a treatment phase of 52 weeks.

Now, this slide shows the percentage of subjects that completed the randomized treatment phase in each of the 18 trials. The trials with a larger font and highlighted in yellow are the trials in the five-study cohort. The blue crosses show the percentage of patients randomized to varenicline who completed a treatment regimen. The red circles show the percentage of subjects from placebo who completed the treatment regimen.

You can see that, overall, patients on varenicline were more likely to complete their treatment regimen than patients on placebo. The two major exceptions are trial 1115 and trial 1072, which are both part of the five-study cohort. And in particular, trial 1072 is the one with patients with a history of schizophrenia.

Now, let me describe briefly the statistical methods used in the meta-analysis. All of the

analyses discussed in this presentation are based on treatment-emergent events, which are the finest events that occurred while on randomized treatment, plus a window of 30 days after treatment discontinuation.

Suicidal ideation or behavior collected on the C-SSRS was analyzed to a percent regression with covariates for baseline history of suicidal behavior, study, and treatment. The other endpoints, which are the SMQs, the overall psychiatric events, and the custom endpoint, were analyzed through Mantel-Haenszel relative risk and risk difference, stratified by trial.

In this presentation, I will only show you the results of the relative risk and not the risk difference because they led to some other conclusions. All confidence intervals are shown at the nominal 95 percent confidence interval, not corrected for multiplicity.

So here are the results of the meta-analysis. First, I will discuss analysis of suicidal ideation or behavior. And later, I will

discuss the results of the other endpoints. So this is a forest plot of suicidal ideation or behavior captured through the C-SSRS questionnaire in the five-study cohort. Remember that this endpoint was prespecified and it was collected prospectively in these five trials.

There were 28 patients on varenicline and 27 on placebo who reported suicidal ideation or behavior based on this questionnaire. The corresponding estimated relative risk was 0.79 and shows no evidence of increased risk of suicidal ideation or behavior associated with varenicline.

The two trials highlighted in yellow is trial 1072, which enrolled patients with a history of schizophrenia, and trial 1122, which enrolled patients with a history of depression. And you can see from this slide that these two trials contributed 48 of the 55 events of suicidal ideation or behavior captured in the C-SSRS. The other three trials contributed only 7 events.

So it is unclear, based on this slide, whether these findings can be generalized to a

population without a history of schizophrenia or depression.

It's also important to note that most of the events captured in the C-SSRS corresponded to suicidal ideation and not to suicidal behavior. This table shows that the C-SSRS captured only two events of suicidal behavior, one on varenicline and one on placebo. And there was 1 additional event of self-injurious behavior captured on placebo. All the other events captured in the C-SSRS instrument corresponded to suicidal ideation.

Now, here is a forest plot of the Suicidal/Self-Injury SMQ, which was collected in the 18 trials. The trials in the five-study cohort are highlighted in yellow. And remember that this SMQ is based on adverse events collected through routine reports in these 18 trials.

There were 11 events recorded among subjects randomized to varenicline and 14 events among subjects randomized to placebo. The estimated relative risk is 0.45 and shows no evidence of increased risk of suicide or self-injury associated

with varenicline.

I want to note that this analysis captured fewer events than the C-SSRS instrument, 25 here compared to 55 in the C-SSRS, even though this analysis included 13 more trials. So to look at the difference between the C-SSRS difference and the SMQ, we compare them in the five trials that use both mechanisms to capture information related to suicidal ideation or behavior.

So the number of events on the C-SSRS are shown on the first row of the table, and the number of events on the Suicidal/Self-Injury SMQ are shown on the second row. So the comparison of interest here is between the rows, not between the columns. And you can see that the C-SSRS collected many more events, 28 compared to 8 on varenicline, and 27 compared to 11 on placebo.

What this suggests is that the Suicidal/Self-Injury SMQ, which is based on routine or adverse reporting, may have lacked sensitivity to capture events related to suicidal ideation or behavior in these trials. But this table shows

that the larger discrepancy between the C-SSRS and the Suicidal/Self-Injury SMQ was observed in trial 1122, which is a trial that involved patients with a history of depression.

In this trial, there were 35 events related to suicidal ideation or behavior captured on the C-SSRS and only 7 captured on the SMQ. And this point is important because the other endpoints that I will discuss in the next few slides were also collected through routine reports of adverse events. And therefore, it is possible that they may also have low sensitivity to capture the events of interest.

So now we will discuss these other three endpoints, hostility, psychiatric disorders, and the custom NPS endpoint. Remember that these three endpoints are based on adverse events collected through routine adverse event reporting.

In this set of 18 trials, there were 27 patients randomized to varenicline and 18 patients randomized to placebo, with adverse events in the Hostility and Aggression SMQ. The incidence rate

was approximately 1.8 cases per 100 person-years for both varenicline and placebo. And the estimated relative risk was close to 1 and shows no evidence of increased risk with varenicline.

Looking at this SMQ on a more granular level, all adverse events in it were recorded as either aggression, anger, or hostility. And there was not a clear difference between subjects randomized to varenicline or placebo.

The next endpoint is the psychiatric disorder system organ class, and this endpoint includes a wide range of adverse events such as depression, hostility, anger, suicidality, and many others. And you can see that it captured many more events, 593 on varenicline and 388 on placebo, with a comparable incidence rate of around 39 per 100 person-years and an estimated relative risk very close to 1 that shows no difference in risk between varenicline and placebo.

This plot shows the incidence rate for the most commonly observed components of the psychiatric disorder SOC, which are anxiety

disorders, depressed-mood disorders, and other mood disorders. And in each one of the components, there was no clear difference between varenicline and placebo.

Finally, here are the results for the analysis of the custom NPS endpoint. Remember that this composite endpoint includes specific events related to anxiety, depression, hostility, suicide, and other psychiatric events collected through routine reports with a minimum threshold of severity.

The overall incidence rate for this endpoint was 9.5 to 9.8 events per 110 person-years with an estimated relative risk of 0.85, and shows no evidence of increased risk associated with varenicline.

Looking at the components of this endpoint, the most common components were agitation, mania, anxiety, aggression, depression, and suicidal-related. And you can see that there are some numerical imbalances between the components, but overall, there is no clear evidence of differential

risk between varenicline and placebo.

So now, I will present a brief summary of this presentation. Out of the endpoints that I presented here, the C-SSRS instrument was the only endpoint that was actively collected in the clinical trials. In this set of five trials, the C-SSRS identified 55 patients with suicidal ideation or behavior and showed no evidence of risk, of difference risk, between varenicline and placebo.

The main limitation of this endpoint is that the majority of the events were observed in the two trials with a history of schizophrenia or depression. And, therefore, it is unclear whether results can be generalized to patients without these conditions due to the few observed events in the trials without these conditions.

The Suicidal/Self-Injury SMQ was based on routine reports of adverse events in all 18 trials and did not show a difference between varenicline and placebo. However, we showed that the SMQ may have lacked sensitivity relative to the C-SSRS to

capture events related to suicidal ideation and behavior.

The Hostility and Aggression SMQ captured 45 total events and showed no difference in risk between varenicline and placebo. The limitations of this endpoint are that it is based on adverse events collected through routine reports and that it includes events of all severities.

Similarly, the psychiatric disorders SOC, which included a wide range of psychiatric events, captured 981 events total and showed no difference between varenicline and placebo. And the limitation of this endpoint, again, is that it is very broad and that it includes events of all severities collected through routine reports.

Finally, the custom NPS endpoint that included selected adverse events showed no difference in risk between varenicline and placebo. And while this endpoint captures only events that meet a minimum level of severity, its limitation is still that it is based on adverse events collected through routine reports. And that concludes my

presentation. Thank you.

FDA Presentation - Natasha Chen

DR. CHEN: Good morning. I am Natasha Chen from Division of Epidemiology II under the Office of Pharmacovigilance and Epidemiology and the Office of Surveillance and Epidemiology, CDER, FDA. I am going to present our review of the observational studies of varenicline's neuropsychiatric risk.

I will first give an overview of the review of observational studies and their findings, then address our concern regarding the available observational data, and lastly provide a review of the appropriate interpretation and implication of the available observational data.

As you have heard earlier this morning, there are five retrospective cohort studies that examines varenicline's neuropsychiatric risk. We like those studies for the inclusion of their use of real-world data and their inclusion of patients with a psychiatric history, which extends the their generalizability of their finding beyond those

available clinical trials.

The outcomes that have been examined in those studies fall into three types. They are, first, neuropsychiatric medical encounters, including hospitalizations, emergency-room department or ED visits, and outpatient visits; second, suicide-related events such as fatal or non-fatal self-harm and suicidal thoughts; third, initiation of antidepressant therapy, which was used as a proxy for incident depression.

Among these, we don't think outpatient visits can well capture treatment-emergent adverse events, and we don't think the initiation of antidepressants is a good proxy for depression because they are indicated for conditions other than depression, and they can be used off label for other conditions. Therefore, we will focus the discussion only to two types of outcomes.

As illustrated in the following slide, none of the review studies find significant differences between varenicline and its comparator with regard to the risk of neuropsychiatric hospitalizations or

ED visits, as well as the risk of suicide-related events. However, we do not find this result convincing because of several study design issues. I will start by addressing our concern on the studies examining varenicline and risk of neuropsychiatric hospitalizations and ED visits.

Among the three studies examining this issue, we first have concern on the comparator group used by Pasternak, et al. They compared the outcome risk between varenicline and bupropion. Given that bupropion also has been associated with neuropsychiatric adverse events, we don't think it's an appropriate comparator because, even if the findings see a lower risk associated with varenicline relative to bupropion, it is not reassuring for varenicline's safety.

Secondly, all the studies use diagnostic codes to identify medical encounters due to neuropsychiatric events, but no chart review was done to confirm that those events indeed happened. Also, as Dr. Winchell mentioned earlier, we have concern that diagnostic codes might not well

capture varenicline-associated neuropsychiatric events.

Lastly, we also are concerned that a medical record might not be the only data source to look for those events because patients' experience of varenicline-associated adverse events might be referred to the legal system rather than medical system.

To sum up our concern on the outcome measures, first, we think the outcome measures in those studies likely underascertain the outcome, and we don't know how many of varenicline-related adverse events was missed in those studies. Second, we believe the outcome measure likely misclassified the true event, and we are not sure whether the events observed in those studies are the right event that can inform us of varenicline's neuropsychiatric risk.

The impact of this limitation is likely to lead to an observation of no difference between varenicline and its comparator, which is actually what we see in those studies.

Moving on to the studies of varenicline and risk of suicide-related events, although there are two studies on this topic, they both are based on the same source data and with overlapping data time frames. We will focus the discussion on the finding of Thomas, et al. because it is the later study and the researcher linked to other data sources to enhance the capture of outcome events. That being said, we still have concern on their outcome measure. In particular, we worry about underascertainment of outcomes.

Although the researcher linked to U.K.'s national mortality data to identify fatal self-harm, 90 percent of the observed outcomes in the study are non-fatal self-harm, which were identified from hospital admission data. Given the social stigma of suicidal behavior, patients might not carry this diagnosis, and they might not even seek medical help.

So we think the outcome is likely underascertained; non-fatal self-harm is likely underascertained, which will lead to the

underestimation of the true risk.

Additionally, the study included data after the U.K. regulatory agency issued a safety update on the potential suicide risk of varenicline. With the publicity of this safety concern, patients who are more prone to suicidal behavior might have been prescribed the alternative treatment. And indeed, in Thomas's study, we indeed see that the varenicline users are healthier than the comparator, NRT user, in that they are less likely to have a history of chronic disease and psychiatric illness, and they also less frequently have previous use of psychotropic medication.

Recognizing this potential for bias due to patient selection, the researcher conducted two additional analysis in addition to their conventional Cox analysis to further account for the baseline differences. Those analyses are propensity score matching, or PS matching, and instrumental variable analysis, or IV analysis.

Unlike Pfizer, we don't think the three analyses showed the same result on suicidal risk,

and I will elaborate my point in the following slide. First, let's look at the Cox regression finding. This shows that varenicline did not have the risk of suicide related to varenicline. It's no difference from the reference group. However, we also notice that the Cox regression suggested varenicline has a strong protective effect of all-cause mortality at three months, which is the exploratory outcome of this study.

Although we recognize the immediate benefits of smoking cessation, we still think three months is too short to reduce the mortality risk to more than half. So we think the generally healthier varenicline group probably played a role in the big reduction of all-cause mortality, which indicates that the Cox regression did not fully account for the baseline differences between groups. A very similar result was seen in their PS matching regression analysis, which means that these analyses still did not fully account for baseline differences.

Before discussing the IV results, I'd like

to first point out that IV analysis produces a different risk measure than the other two approaches. IV estimates risk difference instead of hazard ratio. Therefore, I translated the hazard ratios from the other two analyses to a risk difference. I'd also like to point out how to interpret the risk difference.

Zero means no difference in risk of outcome between varenicline and NRT. A positive difference means varenicline has higher risk than NRT. A negative difference means varenicline has a lower risk than NRT. So let's go back to see the IV result, starting from the finding of all-cause mortality at three months.

We first notice that IV showed the difference in mortality were smaller from the result obtained by their IV analysis than the other two approaches. So we think, because the IV analysis moved the mortality difference toward zero, which is the direction we expect the result to be, we think IV works better in accounting for baseline differences than the other two approaches.

Turning now to their finding of three-month fatal/non-fatal self-harm, we also see differences in their IV analysis than in the other two analyses. The risk difference from their Cox regression NPS matching analysis are both below zero, which favors varenicline, but it is above zero, which suggests that varenicline might have a higher risk of suicide-related events compared to NRT.

Although the risk estimates from IV analysis is not statistically significant, we are concerned about this change in trend. So we variated further on how much we can trust the Thomas et al. IV analysis. I would like to thank my colleague, Matthew Rosenberg, for his help on this task.

Our conclusion is that we are not 100 percent confident their IV result is bias free, but we think it's less biased than the other two approaches, and I will elaborate my point in the following slide.

Before showing more data to support my point, I'd like to give a brief introduction of the

IV analysis. I understand Dr. West has gave us some introduction earlier, but since I have made the slides, please bear with me for just a couple minutes.

So the issue the IV analysis is trying to handle is when you compare outcome between actual treatment group, it is biased by patient selection. In our case, it's like comparing the suicide-related risk between our varenicline user, the blue group, an NRT user, the green group. It's biased because a patient with a high risk of suicidal behavior, those in the red boxes, are more likely to receive NRT. If we use a Venn diagram to depict this issue, it will look like this.

The blue circle represents the estimated varenicline effect on suicide-related risk. When we compare directly between varenicline user and NRT user, this blue circle will carry bias from influence of other factors of suicide-related risk such as patient characteristics, which are represented by the red circle.

So IV proposed instead of comparing outcome

between the actual treatment groups, which will give us this blue-circle by the red circle, let's compare treatment by a surrogate to the -- let's compare the outcome by a surrogate of the treatment, which we call an instrumental variable or IV. And we want this IV to borrow the treatment effect that is not biased and to provide us a better estimation of the true treatment effect.

If we draw this again by the Venn diagram, it will look like this. So the green circle represents IV effect. For an IV analysis to work well, the IV need to fulfill two criteria. First, we don't want this green circle -- we want this green circle, which has a big overlap with the blue circle, which is the true treatment effect, so that we can really see the true treatment effect from the overlap. Therefore, I will need to be strongly associated with true treatment assignment.

Second, we don't want green circle to overlap with the red circle at all, so the IV estimate won't carry bias. So to fulfill this, the IV needs to be independent of all the risk factors

that could influence suicide-related risk. So it's not surprising that a key to a good IV analysis is to have a good IV that fulfills both criteria.

Let's go back to the Thomas's study. The IV that they choose is physicians' prescribing preference, which they identify by their past prescribing pattern. The researcher identified the prescribing physician of each patient and looked back at their prescribing pattern before seeing this patient. If the physician prescribed varenicline more often than NRT, they are a varenicline doctor, and a patient who goes to a varenicline doctor are categorized into the varenicline group. Similarly, if the doctor prescribe NRT more often, they are an NRT doctor, and their patients are in the NRT group.

The researchers indeed provided data to support that the prescribing pattern is highly associated with the extra treatment received by the patient, which means that this IV fulfills the first criteria to be a good IV.

However, we have concerns that the IV they

choose may not be completely independent of other risk factors for suicidal behavior. So we think the relationship between their IV, and treatment effect, and other factors would look like this, that IV will have a little bit of overlap with the red circle. We say this based on the data provided by the author in some theoretical argument.

In the following four slides, I will start addressing this concern using the data provided by the author. When comparing patient characteristics between IV, a side group, we indeed see the differences that we saw earlier between the actual treatment group was reduced.

For example, the proportion of patients with previous chronic diseases and psychiatric illness are more similar between IV-assigned group as well as the proportion of patients who have prior use of psychotropic medication. However, we notice some baseline characteristics still are not balanced between IV assigned group; for example, previous smoking cessation history and the timing of treatment exposure. This raises the concern that

IV might not be independent of all the factors that could influence suicidal behavior.

We also notice that physician characteristics is not captured in Thomas, et al. study. If physicians' prescribing preference are related to their familiarity with current literature and their use of this information, a physician who prefers varenicline because of its high efficacy could be more vigilant to monitor the risk of suicide or depression of their patient because there's no side effect of smoking cessation.

In this case, patients who go to a varenicline doctor will have lower suicide risk, which is unrelated to drug effect. So to put in all information together, we think the IV analysis in Thomas, et al. did not fully alleviate the bias, but at some point reduced the baseline selection problem because we see the baseline characteristics are more balanced between IV groups than between two treatment groups, and also that we see the reduction in IV analysis than the other two

approaches.

But the impact of this limitation and our concern on the IV analysis is that their IV estimate still can be biased by differences in physician characteristics and likely underestimated the true risk of fatal or non-fatal self-harm.

So finally, to sum up our assessment, with regard to the studies of varenicline and risk of neuropsychiatric hospitalization and ED visit, we don't think a finding of no increased risk of this outcome compared to bupropion is reassuring of varenicline's neuropsychiatric safety.

We also think that using diagnostic codes to identify outcome events likely leads to underascertainment and misclassification of the true event, which likely leads to an observation of no difference between varenicline and its comparator.

As for study of varenicline and risk of suicide-related outcomes, two studies indicated negative association, but they both carry bias possibly due to baseline selection. The analysis

that reduces such bias suggests varenicline has a higher risk of fatal and non-fatal self-harm. Although the increase in risk is numerically small, it's likely underestimated because of the underascertainment of this outcome, of non-fatal self-harm. However, the risk estimate was imprecise, and its confidence interval crossed zero. So we think the data are inconclusive.

Lastly, an overarching limitation of our review study is that the outcome examined in that study did not cover the full range of the neuropsychiatric adverse events that have been associated with varenicline in spontaneous case reports.

To conclude, due to the limitations, in particular, the limitation on the outcome measure which likely are underascertained and misclassify true events, we think the observational data precludes conclusion of no association of varenicline with neuropsychiatric risk. We also found it is challenging to evaluate this issue using observational data due to the difficulty in

capturing all relevant outcomes and correctly classifying varenicline-related events; and that it's difficult to avoid the selection of healthier varenicline users because the safety warning came soon after the market of varenicline.

So we believe the ongoing safety trial that Pfizer is conducting right now is likely to offer a better insight to varenicline's neuropsychiatric risk than the available observational study. And this is the end of my presentation.

DR. PARKER: Thank you. We will move on to clarifying questions for the FDA, but we have a new person at the table. And, Dr. Temple, we'll let you introduce yourself. Thank you.

DR. TEMPLE: Good morning. I'm Bob Temple. I'm deputy center director for Clinical Science. Thanks.

Clarifying Questions to FDA

DR. PARKER: Thank you. So we have until noon for some clarifying questions for the FDA. I will ask people to, again, identify yourselves by a nod of the head and a hand, turning your card

sideways. Make sure that Ms. Bhatt gets you in the queue. And remember to state your name and, if possible, address your question to someone specifically.

So first out of the gate here, Dr. Gerhard.

DR. GERHARD: Tobias Gerhard from Rutgers. This is a question for, I guess, Dr. Racoosin maybe, just a broad question of how we are supposed to think about the topic. Are we supposed to look at this in the context of the current label? So basically answer the question, is the evidence presented enough to assure us that the current warnings are not of concern, and therefore should be removed? Or should we think about this de novo in a sense and think about how does this evidence inform the question of whether there is a risk? Because, to me, those two evidence standards are very, very different.

DR. RACOOSIN: When Dr. Brodsky presented his overview of the guidelines for when a boxed warning is appropriate, he described the removal of a boxed warning, that there are no specific

criteria except that the data no longer reaches the criteria that would be applied to make a boxed warning.

So I think that's what you're asking. To make a determination to remove it, we would have to determine that the criteria for a boxed warning are not met. So I think it's an integration of all of the streams of data that you've heard to determine whether that threshold is met or not met.

DR. PARKER: Does that answer your question? Maybe restate the question just to make sure you got the answer, that you have clarity.

DR. GERHARD: This is kind of the answer I expected. It doesn't quite answer. To me, the standard to remove an existing warning seems to require stronger evidence than looking at the data comprehensively. To say the concern that's currently stated is unfounded requires more evidence than the question of, is there a concern about a causal association looking at the totality of the data.

DR. PARKER: So I might just ask, because I

know there's a lot of thought that goes into this on all sides, whether or not the framing of the question that's being put to the committee probably captures what it is you're looking for. There's discussion and then there's choose between one of three. And I'm assuming that the answer lies within that, but maybe we could get some clarity. Thank you.

DR. TEMPLE: This is Dr. Temple. John may want to comment on this, too. I mean, in a certain sense, the standard for putting it in and removing it, they sort of have to be the same. I mean, there's a standard -- whatever that is, it's not that precise -- on when a box goes in. But the reality is that taking something out seems like a big deal. And so it's possible that there is a somewhat higher threshold for taking something out because you've been there and it's been in part of the prescribing information.

So it's sort of obvious that, intuitively, there's a somewhat higher threshold for getting rid of it, and it's very hard to say exactly what it

is. But in a technical sense, we've written the standard for when there's a box. If the standard is no longer met, it sort of should go away. They ought to be more or less the same. The reality is it's a big deal to remove one.

DR. PARKER: I did want to remind people on the committee, certainly, we can go back to the earlier FDA presentation that included the discussion about the black boxed warning that we had prior to the industry presentation.

I did have one question related to that, Dr. Brodsky. Maybe you can answer it or someone else. And that related to how the black boxed warning's presence or absence relate specifically to what ends up in a med guide. That's one question, because I didn't see proposed changes in the materials submitted by industry, but I could easily have missed them.

The other question related to that was, when there is a black box versus when there is not a black box, how that relates to advertising for a medication, and if there is removal, what there is

in terms of advertising, that you had one and now you don't and whether or not there's oversight for that.

Those were two questions I had related broadly to how the public perceives presence or absence of a black boxed warning. Thank you.

DR. BRODSKY: Hello. This is Eric Brodsky, FDA, SEALD labeling team. With respect to both your questions, I will defer to some of my FDA colleagues about the advertising implications and the patient labeling implications in terms of a medication guide. I could speak more broadly.

So a boxed warning is one aspect of the prescribing information to communicate safety information or a safety concern. It's not everything. As you know, there are contraindications, so situations in which one must not use the drug. There's also limitations of use, where there's a reasonable concern about safety or efficacy of the product. There's also restrictions to the indication, so putting something as a second-line use. So a boxed warning is one aspect

of the prescribing information. It's not everything.

With respect to your direct questions about patient labeling implications, the medication guide, and the advertising implications, I don't know if there are other folks from the FDA that can comment on that.

DR. RACOOSIN: So as the medication guide currently stands, it describes the serious risk of neuropsychiatric adverse events. And I think that the language that's in there is consistent with what's in the warnings section as well as the boxed warning. So I can't specifically predict exactly how it would change, but currently, the description is consistent with the description in both the warning and boxed warning.

So again, I don't anticipate, but again, I can't state with certainty, but it seems that the current description would likely not change in the medication guide. There are differences in the advertising, and I am going to defer that to one of my colleagues.

DR. JENKINS: There are differences in the advertising restrictions that are placed on products that have a boxed warning. For example, if it has a boxed warning, that warning has to appear on all the promotional materials, which tends to interfere with things like the handouts, like pens, and pencils, and things like that, where it's very hard to capture the boxed warning. So if the boxed warning goes away, those restrictions would no longer apply.

We have very limited experience, as we've said, in boxed warnings being removed. As far as whether that might be part of an advertising campaign that, "We used to have a box. We don't have a box anymore," I don't think we have enough experience to say what that might look like.

DR. PARKER: Dr. Augustson?

DR. AUGUSTSON: First of all, I want to thank all of the speakers today. These were some really, really great presentations. My question is to Dr. Winchell. So you raised a very, very good point about are we failing to capture what is

actually the significant problems that the consumers are experiencing.

Does the trial that is going on right now, the safety trial, does that increase the sensitivity to capture that or is that something we are still missing?

DR. WINCHELL: Obviously, we hope that it does. It features a tool to solicit from patients a list of different symptoms they might be experiencing. And Pfizer, for interim analysis, had come up with a list of specific terms they were going to include in their composite that perhaps we'll take a closer look at before the final analysis, make sure everything is being captured.

That's what we were hoping it would do. And that's why it might have taken so long for us to come up with how it should be conducted, because that is the aim, and certainly that's our hope. Guarantee, I don't know.

DR. PARKER: Dr. Pickar?

DR. PICKAR: Thank you. To Dr. Winchell -- and it overlaps to actual comments

by industry -- and relate just for a moment, if I may, on the neuropharmacology of this drug. In one brief phrase, abnormal behavioral events, neuropharmacologic drugs have been fundamental to modern neuropsychopharmacology, from mechanisms of drug action to disorders of the brain and so forth.

This is an interesting pharmacologic drug, as you made reference to, and you did as well, sir. It releases dopamine in a more detailed briefing package. Not just releases dopamine. It specifically releases it in the mesolimbic system. The mesolimbic system is where we live, where I used to live, if you're a scientist.

That is the area that disturbs behavior, that results in disturbed behavior in part, as well as reinforcing behavior. That's why it's such a beautiful drug. So it's a tricky drug. It's a partial agonist/antagonist, I assume, which again gives us -- I mean, they are terrific compounds.

So I'm making a circle here, but I want to get to the point of it. Not just public health and statistically, these adverse events affect people

individually, and could be very, very serious. So we recall that brought this whole thing to the fore, was a tragedy. But tragedies do happen, and they happen in individual cases. And they can happen from behaviorally active compounds. Okay.

You said here that it releases dopamine, but no more than nicotine. I don't know -- the pre-clinical data know exactly how that plays out and whether they release it in the same part, number one. Number two is a partial. Does that change the nature of dopamine release? And then even if it's a small amount, the key thing of course is in a susceptible individual, he or she may experience dopamine release different than the average bear. And at the end of the day, we're resulting in what could be very significant side effects.

So question, back to Dr. Winchell, who I brought it up to from the FDA, talked about thinking about, as a partial agonist/antagonist, getting more severe withdrawal, perhaps. Is that where your thinking was?

What is your understanding of why you are seeing these behavioral effects?

DR. WINCHELL: Well, as I mentioned, my presentation was meant to take you back in time to when we first began thinking about this. And at the time, I did think, speculatively, that the phenomenon of precipitated withdrawal, which is a well-known experience among persons physically dependent on opioids who are exposed to partial agonists at the mu receptor, could be at play here. I don't think that this has been extensively evaluated specifically, although I will say that there are certainly pharmacologic differences between the time course of withdrawal in opioids and in nicotine dependence.

Smokers generally wake up every morning in withdrawal, so introducing Chantix at that point, we'd like to think, wouldn't precipitate withdrawal. It was a speculation. I'll let Pfizer comment on whether they have investigated this more closely in animals or in humans.

DR. PICKAR: Any biological understanding of

how this causes what can be very strange effects? And the ones that don't have a name, those are distorted, perceptual. Those are things that, if you're in the world of psychiatry, we deal with, and they're not always the most fun complaints that you have to deal with. They speak to trouble without fully getting there.

The fact that some people have aggressive behaviors would not surprise me for a dopamine agonist. And we've all learned that, of course, from treating Parkinson's patients or whether you use other kinds of stimulants that are very dopaminergic.

But I am just curious and I'm sorry if that's a little off-track. But to me, it's fundamental to understanding what we're dealing with.

DR. PARKER: So I'm going to ask if sponsor has a specific, short, targeted response, that would be great. Otherwise, we've got six more in the queue, and we'll move along. But if you can sort of answer exactly what that is briefly, that

would be great.

DR. WOHLBERG: Thank you. It's an excellent question and I thank you for the opportunity to directly answer it.

If I may have MOA-10, please? What we're seeing here is the release of dopamine in the rat nucleus accumbens after administration of 1 milligram per kilogram of varenicline in the black boxes compared to intraperitoneal injection -- subcutaneous injection, rather, of nicotine, .32 milligrams per kilogram.

You can see the more rapid uptake and offset of nicotine with comparison to the more prolonged effect of the partial agonist, varenicline, which has about a 50 percent ability to release dopamine in a nucleus accumbens compared to nicotine.

You can see that when you combine nicotine with varenicline, you don't see any further increase in dopamine release. And the order of magnitude -- one final point about this is the order of magnitude of dopamine release is about 40 or 50 percent compared to cocaine, which is about

500 percent, and compared to methamphetamine, which is about 2,000 percent. You're talking about a mild shift here.

If I very quickly can see S-247, also that mechanism slide. That continuous level is very much like what you'd see with a nicotine patch. This is a Minnesota Nicotine Withdrawal Scale. And the comment about withdrawal symptomatology, remember, if we go back to efficacy, the efficacy is much greater than placebo. And if you were to expect an increase in withdrawal symptoms because of the increase in abstinence, you would expect to see an increase in withdrawal symptoms, all other things being equal, if that was the case.

But that's not the case. And what we can see on a Minnesota nicotine withdrawal Scale is that there is at no point in time any increase in withdrawal symptomatology compared to placebo, despite that difference in abstinence.

DR. PARKER: Dr. Grieger?

DR. GRIEGER: I have a comment and then some very specific clarification questions. I am quite

impressed by protocol A3051123, which is the phase 4 random controlled trial with a large sample size. What I'm struck with is it has multiple data points. It has visits basically every week for the first half of the trial, every two weeks towards the end of the trial. And then it follows on after the treatment phase is discontinued.

In each of those, there is a structured adverse event scale, which is posed, both voluntary and inquiry, into the adverse events, the Columbia scale for suicidality specifically and also a carbon monoxide test to determine whether or not the individual has resumed smoking again or not. Plus, they have to bring in their pill package to show whether they took it or didn't take it. All those things are subject to a little bit of manipulation.

But you have many of the questions answered with regard to are they stopping the drug, are they taking the drug, are they smoking and taking the drug.

Getting back to the 18 studies in the random

controlled meta-analysis, those are all Pfizer studies. I don't know if any of them have been published anywhere. Did the FDA specifically have each of those studies and all of the data from those studies in coming up with their review of the quality of the analysis or are they relying on a summary of the data provided by Pfizer, basically? And if they had those data, were those data adequate to answer the sort of questions that this prospective study would answer?

DR. ANDRACA-CARERRA: This is Eugenio Andraca-Carrera, statistical reviewer at the FDA. Pfizer submitted one data set that compiled all of the subject-level information from these trials, so we have the subject level data compiled in one data set for all 18. And we also had access to the protocols, to look at the different protocols, and inclusion criteria, and so on for these 18 trials.

DR. GRIEGER: I guess the follow-on to that, did those data sets include questions about adverse events at each visit? Did it include the assessment of whether they were still taking the

drug or had abruptly stopped it? Did it include the carbon monoxide test?

DR. WINCHELL: I'll comment on that. This is Celia Winchell. We have had many, not all, 18 studies submitted to us as final study reports, and many of them in the context of supplemental applications, where we have carefully reviewed the data and incorporated those new studies into labeling.

So I can tell you that the design of the trial, the frequency of visits, the ascertainment of smoking status, medication accountability, all of those features were included in those trials as well. Whether all of them have the data presented in a way that makes it easy to link smoking status at the time of a particular event and so forth, not always, and the analyses were not always presented in that fashion.

What they lacked was a tool to specifically solicit these types of events. That was included only in, as far as I know, the depression trial that we recently reviewed. And you saw that we had

a higher rate of, I believe it was, regression events in that trial compared to other trials, possibly because they were solicited.

I don't think that any of the trials, even including the postmarketing trial that's underway, is capturing the full patient narrative in which they describe to you in a paragraph or two what's going on with them. But we hope that we're capturing enough information to get a sense.

DR. PARKER: Dr. Morrato?

DR. MORRATO: I think I can redirect the question I had from this morning to the FDA and it's sort of follow-up with the last couple of questions. I am just trying to wrap my mind around the differences between case ascertainment and the new trial data that's being presented versus what's occurring in the ongoing study in which we are awaiting the report.

So as others have expressed and you as well, I am concerned about the reduced sensitivity and specificity on the current data and, therefore, implication you have no bias and so forth.

So do you have a slide that's sort of a side-by-side comparison of what is being collected in these existing trials versus in the new one or key differences? Or is it simply, as you're saying, I think, the main difference is prospectively soliciting key endpoints in a systematic manner? I'm just trying to understand what's really the difference, not just the scale, but I think I'm also hearing from you how it's being collected and the frequency by which it's being collected is important, too.

DR. WINCHELL: That's the key difference, is that it's being solicited. I don't think the frequency of visits is very different. Each of these smoking cessation trials generally have people come visit every week or two for the first several months, and then they may be spaced more widely. And at each visit, they are given an opportunity to volunteer any problems that they may have been having. And those are captured as adverse events.

What's different about this trial that's

underway is that we asked Pfizer to develop a tool that would, a structured interview if you will, get at these areas of difficulty that people might be having and better ascertain them.

DR. MORRATO: So from your point of view, then, I know it's not unblinded yet, but the 4.5 percent reporting rate that's being observed so far in the interim analysis would be encouraging evidence that it's soliciting at least as designed, a certain rate of cases? Is that fair to say? So it's picking up what we thought you might be picking up, at least, I mean, in a quantitative way?

DR. RACOOSIN: Right. So I think that the fact that there is a measurable incidence of the primary endpoint, and at a level that was considered by the data safety monitoring board to be adequate to go ahead with what the planned enrollment was, rather than add additional patients, suggests that enough events are occurring that we should be able to make some conclusions about that.

DR. WINCHELL: Just going back quickly, I think in the early part of this development program, the approach for ascertaining adverse events is the typical approach that is used in randomized controlled trials, a general question about how patients are doing and that sort of thing. And I think Dr. Andraca-Carrera's comparison of what was observed in the C-SSRS compared to what was observed with the SMQ, that difference, reflects some of that difference in soliciting versus just generally asking.

DR. PARKER: We have several in the queue, so I'm going to ask people, if they can, to make them very pointed so we can get to as many as possible. Dr. Battisti? Thank you.

DR. BATTISTI: Hi. Thank you. Two or three quick questions. One, it's interesting -- or maybe some comment from the Office of Biostatistics. In our briefing documents, there was a specific recommendation made by the Office of Pharmacovigilance as well as the Office of Epidemiology against making changes. And there was

an absence of a recommendation from the Office of Biostatistics regarding the meta-analysis. Is there a recommendation?

DR. ANDRACA-CARERRA: My only job was to review the data for the meta-analysis and to present the results, so I don't believe that the Office of Biostatistics has any recommendation. Just our job is to present the data and let the committee discuss.

DR. BATTISTI: So contrary to other offices with the other data, it is common to have a specific recommendation.

DR. PARKER: Any comments from the FDA?

(No response.)

DR. PARKER: Noted.

DR. JENKINS: Maybe it would help if you could restate the question. I'm not really sure what you're asking.

DR. BATTISTI: Well, I guess it's confusing. In some respects, the FDA is providing us the data in making a recommendation of what we should do with the data, but it's inconsistent. Maybe that's

just a comment, then.

My other question is with Pfizer. It's interesting. Is it intended to, in the potential label change, not include sleep disorders and other sleep disturbances, even though there seems to be a stronger causation analysis supporting that? And those can obviously be serious as well.

DR. PARKER: So specifically to that, we have asked to actually take a look at those. So let's take a look at those and be very clear on that when we come to the discussion of the issue related to the sleep disturbances and what we're going to do with that. And we'll take a look at the documents themselves, at what's being proposed.

DR. BATTISTI: Then my last question is -- and I guess this would be for the FDA in general -- the last three sentences of the current boxed warning states language that could be taken as being promotional in nature or misleading in terms of what data there is to support that.

Is that common to have language like this in a black boxed warning? I'm a pharmacist as well,

and I have not seen that on any other black boxed warning.

DR. PARKER: So maybe we can ask the FDA if there's anything in particular about the language specific to this black boxed warning that is unique or that should be something that you'd like advice or input on, specific to the exact content in those three sentences. And if not --

DR. BATTISTI: Thank you.

DR. RACOOSIN: It's generally not typical to include benefit in a boxed warning, or discussion of benefit, or weighing the risks and benefits.

DR. PARKER: When we get to our voting and discussion this afternoon, we'll make sure that, as a committee, we understand what you specifically want most advice on relating to that and other points about the exact content. That's great.

Dr. Budnitz?

DR. BUDNITZ: Yes, a clarifying question. The sponsor -- Dan Budnitz from CDC -- suggested that -- in their slides, they quoted some FDA guidance and suggested that there needs to be more

definitive causality, a specific adverse drug reaction, not just a suspected adverse drug reaction, to be included in a boxed warning. But the earlier FDA slides suggested that there were other reasons to put warnings that may not be definitive in a black box.

So I just wanted to hear FDA comment on is there a different level of causality that's required to put something in a black box than to put in the precautions section.

DR. BRODSKY: Hello. This is Eric Brodsky, SEALD labeling team, FDA. If you're referring to one of the applicant's slides, it had some slides about pharmacovigilance. And those refer to regulations for investigational new drug applications reporting, so that's pharmacovigilant reporting. That's very different than labeling.

So from a labeling perspective, an adverse reaction is an untoward event or an undesirable event with a possible causal relationship to the drug, although a causal relationship does not have to be proven. So there's a different level of

evidence, and I would recommend you go by the labeling recommendations for the prescribing information because that's the topic of the boxed warning and the labeling.

DR. BUDNITZ: Thank you. So just to follow up, to clarify. So for our interpretation of labeling for the boxed warning, we should use the pharmacovigilance definitions of adverse reaction or suspected adverse reaction?

DR. BRODSKY: So from a labeling perspective, one would use the labeling regulations, which I stated before, and I talked about the definition of serious adverse reactions or contraindications, also the warnings precautions guidance, as I stated.

So to back up, there are three general reasons to include a boxed warning. But as I stated, there's lots of flexibility according to the guidance recommendations, including if there's an important warning to a prescriber, which could include a clinically significant adverse reaction or a unique benefit/risk consideration applicable

to one drug and not its class.

I should also note from the regulations, the boxed warning regulations, a boxed warning can be included as a result of only animal data. You do not need clinical data to include a boxed warning. And we've done that several times in the past, embryo fetal toxicity that we've seen in animal studies, but we didn't see anything in pregnant women. Typically, there are not many pregnant women in clinical trials.

So the recommendations for a boxed warning are flexible.

DR. BUDNITZ: Thank you.

DR. PARKER: Dr. Temple?

DR. TEMPLE: You don't have bright lines on causality. I mean, things are reasonably likely. I mean, there's all those phrases. I think the idea for a boxed warning is you should be pretty convinced that the drug actually does this. But animal data could convince you that there's a risk, as was said.

I think, as you heard from Celia, people

found the individual case reports with rechallenge and all that stuff pretty convincing. And that was the basis for it. You can always debate how convincing something has to be. You can ask does this occur spontaneously in the absence.

We take things like agranulocytosis or Torsades de Pointes, which really don't mostly occur in people unless there's a drug, as evidence of causality, even if there's not a controlled trial that does it.

So they can be convincing. That's part of what you're being asked about; when does other data contradict that?

DR. PARKER: Dr. Emerson?

DR. EMERSON: Just a quick question for Dr. Chen on the observational studies. Do you have any idea of what the R-squared was both in terms of the variables that they were using to assess how much they were excluding in their instrumental variables the other predictors, or in the propensity score, how predictive the propensity score was actually of the tendency to treat? Is

that quantified anywhere?

DR. CHEN: I'd like to clarify the question. So are you asking what's the covariate they put into the model, associated?

DR. EMERSON: So much of this observational data relies on the fact that there's no unmeasured confounding. But if the measured confounding predicts very little of the outcomes, either of the propensity for the treatment or that -- then it's not very convincing. So I was just asking how predictive that is.

DR. CHEN: Yes. I understand. I didn't find the R squared in the published data, so I couldn't comment on that.

DR. PARKER: Dr. Michelson? Okay.

We will now take a break for lunch. We'll reconvene in this room at 1:00, at which time we will begin the open public hearing. We ask that you take any personal belongings you may want with you at this time.

Panel members, please remember there should be no discussion of the meeting topic during lunch

among ourselves or with any members of the audience. Thank you.

(Whereupon, at 12:07 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:03 p.m.)

Open Public Hearing

DR. PARKER: Good afternoon. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing of the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with a sponsor, its product, or, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance of the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial

relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium -- I believe has already stepped up to the podium -- and introduce yourself? Please state your name and any organization you're representing for the record. Thank you.

DR. LIGHT: Thank you very much. Good afternoon. My name is Richard Light. I am representing my company, Princeton Research Services. We have independently undertaken an assessment of the FAERS data for varenicline, and I have no conflicts to report. My company has been providing analytical reporting services to major pharmaceutical companies for over 20 years, and we undertook this evaluation to try to provide the committee with a perspective on the FAERS data for varenicline.

We're going to use three treatment groups, if you will, or groups of treated patients. And the comparative populations that I'll employ in this evaluation are nicotine replacement therapy, bupropion, and we will of course look at varenicline. My thesis here is that the safety signals observed for varenicline early on in its marketing are present still and have remained unchanged.

This is an effort to show you that the three populations are fundamentally similar. They had

similar proportions of females and males. The age statistics were similar and the age distribution was similar. However, there were important differences across the drug populations also. This highlights some of those differences.

For the bupropion, as you can see, there was a higher proportion of deaths. Bupropion, I should mention, was stripped very carefully of any use of the drug for depression. We stuck very carefully to smoking cessation. The selection process involved using the trade name indications in the database and adverse events that suggested the drug had been used for smoking cessation.

The outcomes here are different as well and worth pointing out. Bupropion had a much higher proportion of hospitalizations reported, and it is of note that lawyers contributed significantly to the varenicline reports. I have examined the data both with and without their contribution and, fundamentally, things are the same.

The other interesting aspect of this is here are the report dates as a function of time. And in

2010, in two weeks in July, 28,000 case reports were reported to the FDA database. This was more than had been reported in the prior three and a half years, and I have no explanation for this. As a result of this, temporal changes with time became very difficult to discern, and I ended up using initial manufacturer dates for the calculations.

This is a graph of the reporting, seen two different ways. The FDA initial report date is in red here, and the manufacturer's reporting data is in blue. You can see the spike in the third quarter of 2010, and it probably reflects cases that were observed over the -- well, it does reflect cases that were observed over the preceding three and a half years.

This slide is an effort to show that the seriousness of the cases is a function of gender, changed. That is, non-serious reports generally had a greater proportion of women. By the time you get to serious reports, the proportions were approximately equal. And when you get to deaths, the varenicline deaths have about threefold more

males than females in the population.

Next slide is an effort to show you the top 12 reported adverse events for varenicline. And interesting, one of the clinical trials this morning that was mentioned apparently saw sleep abnormalities as the principal adverse event. But in the labeling and also in the FAERS database, nausea and vomiting is the most frequently reported adverse event for varenicline.

You can see here that 8 of the 12 most frequently reported adverse events are of psychiatric origin. Two of them are of neurologic origin. Essentially, this top 12, if you will, reflects the concern the agency had in 2007 when they recognized the frequency of significant psychiatric events.

So here we have depressive disorders, neurologic signs and symptoms. Abnormal sleep patterns, we have already talked about and have been acknowledged by the sponsor as being a recognized event. But as well in this list -- and you can see it here -- are suicidal and self-

destructive behavioral problems that have a very high fraction with respect to nicotine replacement products, a very high proportion.

This is almost a 20-fold increase in these events compared to nicotine replacement products. And for bupropion, the fraction is less but still significant. We regard any number over 2 as a significant or a signal worthy of attention.

This was an effort to look at nervous system and psychiatric case reporting by year for only the serious reports and deaths. And as you can see, there's a lot of noise in the data. The dotted lines are their proportions that are seen for each of these things.

You can see that from inception to perhaps 2010, the range for psychiatric events with varenicline went from approximately 40 percent to 70 percent of the cases. For bupropion, the proportions ranged in the 40, 50 to 60 percent range. And for NRTs, they were a little bit lower, but still in roughly the same range.

Notice this scale is tenfold higher than

either of these two, so we're talking for absolute terms in something that is more than a tenfold increase with respect to these other two drugs.

This is an effort to show the time dependence of suicide and self-injurious behavior that was observed in the database and completed suicides both as an absolute and a relative expression of the total number of events observed for serious cases and deaths in toto.

Once again, varenicline has the highest proportion of suicide and self-injurious behavior. And when completed suicides are viewed, likewise, the proportion is almost twofold higher than bupropion and many-fold higher than that observed for NRTs.

I'm going to skip to the chase here. These are ratios of varenicline with respect to NRTs and bupropion. This is for all cases, but more interestingly, this is for the serious cases and deaths. And the adverse events that are of concern to the agency and the sponsor are all listed here. These were the top hitters with the highest ratios.

They're the same ones that were observed early on.

So in conclusion, what I have found is that the most frequently reported adverse events for varenicline are in the psychiatric disorders SOC. Suicide and self-injurious behavior remains a significant safety signal. And compared to NRT, varenicline has markedly different AE reporting rates for psychiatric events. And compared to bupropion, there's a broader distribution of events, but still significant increased reporting rates, relative reporting rates. Thank you very much.

DR. PARKER: Thank you. There are individuals who have chosen to make a joint presentation. These are the speakers 2 through 7. Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record. Thank you.

MR. MOORE: Yes. Good afternoon. My name is Thomas Moore. I am senior scientist with the Institute for Safe Medication Practices. I will

assure you, I have been compensated by nobody for the preparation or delivery of this presentation today, but I have indeed been a consultant in the legal system.

I think the critical policy issue here today is what is the role of adverse event reporting and the scientific weight of that, and how does that compare to observational studies, clinical trials, and meta-analysis of clinical trials?

Now, there are two studies that address this. The top one was published by the FDA; the bottom one was actually written by me. And we got very similar results. They did 2010. I did 2009. The critical fact that comes is that when it comes to safety warnings, the principal source, overwhelming all other data, postmarket or spontaneous reports, and rarely do we see observational studies used at all.

If we go to boxed warnings, which I did in my paper, we find that about 75 percent of new boxed warnings are based on spontaneous reports and none on observational studies.

We can't really take time here to talk about the strengths and weaknesses of each method, but the reason -- this is a merit system, to tell you the truth. The reason why we principally rely on adverse events is because they're they only method that's designed specifically to identify drug adverse effects.

So let's go on and turn to Chantix. Here are just some totals. And what is a large total like this? And these categories are standard, but they clearly overlap, as we'll see. So let's take the smallest one, in many ways a difficult one, psychosis.

The reason psychosis is interesting is that when a person starts hearing or seeing things or getting special messages for them on NPR, these cases are going to be observed. be a result of smoking cessation. So it's a good one to track so we can watch how one of the Chantix side effects tracks across other classes of data.

So we start with a plausible mechanism of action. Of course, we know it enhances dopamine.

And what do we know about antipsychotic drugs? They are dopamine D2 blockers.

The next question you should ask is, well, if we never saw anything in clinical trials, we'd be a little worried. But on the other hand, we don't expect to see a lot. So if you look at the NDA, which is about 3,000 patients, you'll find you had two pretty clearly reported psychosis cases. How many were overlooked and never quite got into the NDA, I don't know.

So let's go to a third source. In New Zealand, they have a different approach to postmarket surveillance. And they monitored a whole patient cohort. So how many psychosis cases did we see? It was about the same size as the NDA, in fact, around 3500 patients. They had three cases, no previous history of psychosis. And they had longitudinal follow-up. And so they knew that, on discontinuation, they all got better. They never had psychosis before. They were hospitalized. And they recovered on discontinuation.

So that's one chain for taking the adverse event reports and looking at causation across the data sources. The other way -- and you saw this earlier, so I won't spend too much time on this, which is we can assess individual cases. We saw many cases where there was no psychiatric history. Symptoms early in treatment mean that we get the temporal relationship easily, but it has another drug safety implication here because it seemed to start even before people reached the full titrated dose. It means that if we discontinue this patient, we are going to probably stop that side effect in its track. And we have, as we have all seen before, dechallenge and rechallenge.

Now, let's look at the complexity of the case. And there was a very good presentation from the FDA this morning about how complicated these were. If we look at the statistically significant effect -- we're calling it sleep disturbance -- what do some of them look like? Some of them are the most horrifying dreams that people can actually not speak about. They then go

into uncontrollable rage, but it was very common to be a threat or violence to someone else, but then to themselves. So in this one subset of cases, we see people just careening out of control in this unusual and almost senseless matter.

Now, I'll give you the simple version. You've got the more complicated one. This is just a total of two event terms, which are homicidal and suicidal ideation. And as you can see -- and it's the entire period, from 2007 through, my data, 2013.

What you'll see is here they are, just ranked, very simple ranking. We'll get to more sophisticated ones later. But basically, it means we have really nothing. We have never seen anything like this. So we're not really talking about how we interpret a flickering adverse event signal. We're talking about where is the most pronounced data for a psychiatric side effect that those of us who do this all the time have virtually never seen for any other drug.

The final part of this is it doesn't rely on

one investigator. The person before, who I never met, saw the same sort of thing. In your package were two reports from the Office of Surveillance and Epidemiology. Just published a week ago was a study in the U.K. system, which is a yellow-card system with physician reporters; New Zealand, the patient monitoring study. French has a regional pharmacovigilance system. And QuarterWatch, the publication I detected, has of course seen it all along.

So the truth of the matter is, everybody has seen it. It is over every period of time. You can adjust it any way you want. In the 10 or 15 years that I've done adverse event analysis, we have never seen a case as serious and as clear as this drug.

Now, I was here this morning and wondered -- I was listening to some of this -- to be frank, whether I was in Alice in Wonderland. So we have a manufacturer who, let's face the facts, paid 2,500 Chantix victims of neuropsychiatric side effects rather than try a single case in court.

And now we hear a scientific presentation that ignores most of the evidence that says it doesn't cause psychiatric side effects. It seems to me this committee is being asked to ignore the adverse event data that supports most major safety regulatory actions after approval and believe flawed observational studies with no statistically significant results.

I thought there was an excellent statistical analysis this morning, but I think it omitted what I regard as the single most important control, which is, if you have not disproved the null hypothesis, do you have any evidence that if there was an effect, how are you avoiding type 2 error? How do you know you just didn't do it properly?

The last thing you have to conclude if you want to remove the label is that thousands of people working through four or five different types of national event systems that reported unusual experiences they have never seen before and are experienced medical professionals, that all of those people, they were all wrong.

So my last point is warnings have a real purpose here in drug safety. They prevent harm. Symptoms often start early, often in many, many cases, long before reaching the full titrated dose. And discontinuations really do stop a spiral that we've observed in case after case into really catastrophic adverse events.

So that concludes the first presentation here. Can we put the second slide set up, please? We need speaker number 3. Yes.

I am presenting these slides on behalf of a colleague of mine, Curt Furberg. Here is his disclosure. He's also been a member of the drug safety committee here. He's professor emeritus at Wake Forest University, and he was an expert for the plaintiffs, and he was not compensated for any of his work for this presentation.

Now, Dr. Furberg's approach to this is he would like to review peer-reviewed scientific studies of which he is part co-author. The first of these is thoughts and acts of aggression and violence towards others reported in association

with varenicline.

Now, what is the purpose? This is a case series study, and it is possibly the only one we know of that looks at what does a Chantix aggression violence event look like? Does it have distinctive features that would let us understand the difference between that and an ordinary violent act?

So we two sets of a causality criteria were applied to examine this series of 26 cases. The four unusual characteristics of this are shown here, and we will probably try to come back to them as well.

So here is the next study, prescription drugs associated with reports of violence towards others. What's the difference? That was a 26-case series. This case, let's take all-comers, and let's conduct a proportionality analysis to compare reports of violence across all the drugs, including those cases occurring in patient populations -- be terribly surprised to see about some violent act, such as individuals with an underlying diagnosis of

psychosis that was unrelated to drug treatment.

We use disproportionality because that adjusts for the fact that all across these drugs, we have different levels of exposure. We have different levels of reporting. So we will look at the proportion of reports for this very unusual, distinctive side effect.

So this is what we found. We looked at all drugs. You can see there are about 1,500 cases that we found, and these are pretty hardcore violence terms, possible exception, homicidal ideation. And here are the results. We have really three measures of variable back to the same thing from the previous presentation. We have never really seen anything like this drug. You can see 18 times more cases than would be expected if they occurred randomly. It is also first using the chi square measure of association. All 31 drugs that we felt had an association were p 01.

If you look at cases, 408. It just simply dwarfs it. So it doesn't really matter a lot how you count it. The point I am trying to make to

this committee is, in 10 or 15 years of doing this kind of work, we just have not seen anything like this drug.

So let's go on to the next peer-reviewed study, suicidal behavior and depression. These are different endpoints, and they need to be studied in a different way because, as you have heard previously, these can occur in the smoking population, and we would expect a higher incidence in a smoking cessation population, not based on the properties of the drugs, but based on the fact that individuals with this health status are more likely to smoke. But in this case, we'll limit the analysis to a patient population that's the same across all three drugs. We will compare smoking cessation treatments.

Here, we used a different statistical technique. It's somewhat similar to proportional reporting, but this one is the reporting odds ratio. The really nice factor about using this disproportionality measure is it gives us some confidence intervals. So if you look at the forest

plot here, you'll see bupropion is elevated. And we would agree, and the FDA has put a warning on it. But once again, Chantix is much worse.

Now, this is compared to nicotine replacement. If you compared it to our antibiotic control, just to have some pick-up noise, the odds ratio is, like, 36.

So here is another study. The key item here is we've changed systems. We're going to the United Kingdom yellow-card system, a type of adverse event reporting system. And so let's take a look at the published data that we extracted from the yellow card.

Now, these don't add up because you could have had multiple terms, and to keep it simple, I didn't put the whole table in here. But once again, you have market share up at the top, which we were not able to get for the United States. But what you can see, once again, is we don't have anything like varenicline. Look at the 22 completed suicides, nicotine, zero; 6, bupropion. Now, you have to do the middle denominators in your

head here.

Suicide attempts, 46, varenicline. Here is nicotine replacement, 1. Now, once again, these are mainly coming from U.K. MDs. These are experienced observers who are not going to go turn to a yellow-card system, and fill it out, and send it to the MHRA if they didn't think they were saying something.

So the last study refers to something that was a citizen's petition, but is not a question here today. But the petitioners and myself object to promotional information in a black boxed warning, stating that the health effects of smoking cessation are immediate, which is true when generally speaking characterization of the literature, but never been demonstrated for this drug. And in fact, the most immediate frequently cited benefit are cited cardiovascular events. And so Dr. Furberg was co-author of a meta-analysis of the 14 trials that were then available.

Their result was that this is going the other way. There are no immediate health benefits

of this drug, as far as I know, that can be detected. But when we look at the most important risk where we would expect an immediate benefit, it's going the other way. So I thank you and we will go to the next speaker.

DR. PARKER: Thank you. Will speaker number 4 please step up to the podium, introduce yourself, and state your name and any organization you're representing for the record? Thank you very much.

DR. DOAMEKPOR: Thank you. Could I have the clock started at six minutes, please?

Good afternoon. My name is Lauren Doamekpor and, and today I am speaking on behalf of many members of the Patient Consumer Public Health Coalition. The coalition includes large and small nonprofit organizations across the country that are united to ensure that medical treatments are safe and effective and to enhance the scientific and public health focus of the FDA.

The coalition does not accept -- well, we don't have paid staff, and we do not accept funding

from any outside sources such as pharmaceutical companies or law firms, so I don't have any conflicts of interest.

Smoking kills thousands of Americans, and we agree that Chantix should be an available option for smokers who want to quit. Last week, these five major national organizations filed a citizens' petition for a stronger black boxed warning for Chantix. We agree with those organizations that the black boxed warning is essential and should be improved, not weakened.

The sponsor identified five observational studies and two meta-analysis studies showing no statistically significant differences in various psychiatric adverse effects between Chantix and other smoking cessation drugs. The sponsor suggests that this evidence supports the removal of the black boxed warning for serious psychiatric adverse events.

You need to consider whether the meta-analysis and observational data that the sponsor has identified prove that the black boxed

warning is not needed. The studies in the meta-analysis share the same methodological flaws. They do not assess all four serious psychiatric side effects that have been reported for Chantix: suicide behavior, aggression and violence, psychosis, and depression. And the value of a meta-analysis depends on what studies are included, but no justification was given for the inclusion and exclusion criteria using the two meta-analysis studies.

One of the meta-analysis studies included only five studies, and the studies did not assess hostility, aggression, depression, or psychosis. And it included two studies of smokers who were previously diagnosed with schizophrenia or depression. In other words, patients who were already suffering from delusions, uncontrollable thoughts, or depression before taking Chantix were studied to see if Chantix caused those psychiatric symptoms.

Those two studies should have been excluded from the meta-analysis since a meta-analysis is

intended to combine studies that are similar in terms of study design and outcome measures. That left only three other studies of smokers who were not previously diagnosed with mental illness, and yet, there are at least 14 other studies that should have been considered for the meta-analysis.

The observational studies also had fatal flaws in study design. They didn't analyze all psychiatric side effects. They only analyzed psychiatric hospitalizations, even though 82 percent of the four serious psychiatric side effects seen in adverse event data did not result in hospitalization.

The British Medical Records study, Thomas et al., only examined suicidal behaviors and depression, but nearly 47 percent of the study population had present or previous use of antidepressant medication. It was obviously not a very representative sample at all. The Danish Medical Records study only captured hospitalization and ER visits for the first 30 days after Chantix use was initiated.

So in conclusion, because of the very serious flaws of these studies, they do not prove that Chantix does or does not increase psychiatric side effects. From a scientific and public health standpoint, these studies do not provide an assurance of safety that patients need and deserve.

We strongly urge you to consider that the FDA keep the strongly-worded black boxed warning and delete the misleading conclusions regarding the meta-analyses from the Chantix label. Thank you.

DR. PARKER: Thank you. Will speaker number 5 step up to the podium, introduce yourself, state your name, any organization you represent for the record? Thank you.

MR. GRAEDON: There are two of us. Could you reset the clock, please? I'm Joe Graedon. I'm a pharmacologist.

MS. GRAEDON: I'm Terry Graedon. I'm a medical anthropologist. We have spent 40 years writing the People's Pharmacy books, newspaper columns, and doing the People's Pharmacy radio show on public radio. We have not been paid by anyone

to come and testify today.

MR. GRAEDON: Our website reaches over a million people every month. We started receiving a signal about Chantix, varenicline, in 2007. Initially, it was a trickle, and then it became a stream, and then it became what we would consider a flood. We now have over a thousand messages in the form of comments on our website, e-mails, and letters.

MS. GRAEDON: We really resonated with Dr. Winchell's presentation this morning because so many of the reports that people have spontaneously posted on our website are so similar to what she was referring to, and we're going to read a couple of them.

Here is one that was received on October 18th, 2007. Lynn says, "A dear friend committed suicide four months ago after taking this drug. He was never depressed before. He was a loving father, and grandfather, and a former Marine. I'm afraid the people who write you about a similar experience may be just the tip of the

iceberg. Shouldn't the manufacturer be put on notice?"

MR. GRAEDON: Perhaps many of you have heard the phrase, "Statistics are people with the tears wiped away." We are speaking on behalf of hundreds or perhaps thousands of people who can't be here today. This is a story that we received back in that same time period.

"I am in my sixth week of Chantix and am severely depressed. My doctor is taking me off of it. I have no history of depression and am miserable and frightened at how sad I feel."

MS. GRAEDON: The next story I'd like to read was received just a couple weeks ago. This woman writes, "My husband's best friend, another soldier, started taking Chantix to quit smoking on Wednesday. Sometime Sunday evening or early Monday morning, he murdered a 17-year-old recruit and shot himself in the head.

"He was the sweetest, kindest, gentlest, and most non-aggressive soldier I ever knew. My husband met him in recruiting school, and he was

such a smart, talented person. We are still struggling with what has happened. But after reading stories about Chantix, black-outs and violent rage, that is the only explanation I have.

"Our friend had been drinking over the weekend, so I don't know how much that contributed to his psychosis. Either way, this medication is dangerous. Two lives were lost for no reason."

MR. GRAEDON: Many of the cases of violence that we have received -- and there are many of them -- are in association with alcohol. "I was at the end of my second week taking Chantix, first week as a nonsmoker, when I realized how seriously depressed I had become. My emotions had been off the scale from crying to yelling to feeling totally helpless. I have twice before quit smoking cold turkey and never felt so depressed."

Finally, "Last night, my boyfriend became so violent I was afraid he was going to hit me or my daughter, who stood between us. She is 22. He threatened to burn down our mobile home. He also tried to kick me out. I realize that he started

changing in the last two weeks, a little after he started taking Chantix. He has never acted like this before.

"He was so threatening. He said cruel and hateful things. My boyfriend drinks beer. I am anxiously awaiting his return from work so I can tell him he needs to stop taking this drug. There needs to be a warning about this or a stopping of this drug. If nothing else, this can ruin relationships that were going beautifully."

When I asked my mentor, Professor Ed Domino at the University of Michigan, one of the world's foremost authorities on cholinergic drugs and mechanisms, how this could possibly be happening, he reminded me of Dr. Carl Pfeiffer's hypothesis that when you occupy nicotinic receptors, you disrupt the balance between nicotinic and muscarinic receptors. And if muscarinic receptors take over, it increases the risk of depression. We propose that as a possible area of research.

Finally, we would like to see the black boxed warning strengthened to include a warning

about alcohol.

MS. GRAEDON: It may be necessary for some entity to do further research on the potential for interaction between alcohol and varenicline, but this is definitely a signal that we have gotten strongly from the People who are reporting on our website.

MR. GRAEDON: Thank you for your time.

DR. PARKER: Thank you. Speaker number 6, please step up to the podium, introduce yourself, state your name and organization for the record, please. Thank you, number 6.

MS. WITCZAK: Good afternoon. My name is Kim Witczak, and I am a concerned citizen. And I traveled here from Minneapolis. I am here on my own time and dime. As part of my remarks, I am going to show a brief video and then I will comment after.

(Video played.)

MS. WITCZAK: Today, October 16th, I should be celebrating my 21st wedding anniversary, but my husband, Woody, died 11 years ago of an undisclosed

drug side effect. Ever since then, I have been representing the voice, voices of families who live every day with the consequences of a failed drug safety system.

My husband was given the antidepressant Zoloft, off label, by his GP for insomnia. Five weeks later, he hanged himself by the rafters in our garage. Woody wasn't depressed, nor did he have a history of depression or any other mental illness. And he wasn't a smoker.

Woody did what most Americans do, put their faith and trust in their doctor and assume that the FDA-approved drug being prescribed will help more than it will harm. At the time Woody was given Zoloft, there were no warnings about the risk of suicide or for the patients to be closely monitored. Therefore, a meaningful conversation never happened because a big piece of the puzzle was missing in order to truly assess the risks associated with taking this powerful, mind-altering drug.

Let's be honest. The unsuspecting American

public is the real clinical trial. We are not a number or a percent or a statistic. Like each of you in this room, we are real people with real lives. In my research, I was shocked at all the real-world experiences that had been reported to the FDA, including the 26,000 reports that Pfizer reported improperly.

Here is what Pfizer calls adverse events: 150 completed suicides, 156 cases of severe depression, 102 reports of hostility and aggression, and 56 cases of psychosis. And yet, with less than 5 percent of adverse events being reported to the FDA, this really is just the tip of the iceberg. But what we should really be concerned about is what lurks below the surface, those adverse events that never get reported to the FDA.

We all know people who need this information and turn to the internet to report, such as we just heard, and to look up their side effects. But then, we are called anecdotes, and that's seen as scientifically valid. However, collective

anecdotes are data points and cannot be dismissed.

Let me ask you. Do you find it ironic that the voices you are not hearing from today are the 2700 victims who are all silenced in their settlement and cannot tell their stories publicly? And yet, in the antidepressant hearings, it was victim after victim who were able to tell their powerful stories to contribute to real public safety.

This quote from someone who settled says it all, "I sincerely wish I could tell my story publicly, but like the other 2700 people who accepted Pfizer's settlement, I am bound from saying anything. It isn't fair that my FDA, which supposedly protects me, continues to let this drug stay on the market, which can hut others."

So why is it so hard to get the full truth about the drugs we put in our bodies? In order to fully evaluate and make informed decisions about the calculated risks we are willing to take, we need to have all the information.

Death and suicide are not the kind of risks

that most of us are willing to take. I am almost certain the mom who wanted her 27-year-old son to quit smoking would have wanted to know the risks when he started to complain about not feeling right. Instead, her son hanged himself three weeks after starting Chantix. Even if a risk is really rare, that tiny risk may be somebody's child, or mother, or friend. It becomes their 100 percent.

So I am here today to ask you to be our watchdog and fulfill your mission to protect public health. More than just ensuring safe and effective products reach the market, we also trust you to monitor them for continued safety.

We are all missing part of the story if we only hear from the sponsor and their selected studies, and I appreciated some of the additional FDA studies this morning. And I also would hope that you would read that citizen petition because there's a lot of other really good data in there.

But by relying on one-sided data while ignoring other evidence, we placed consumers at risk. As was uncovered in the antidepressant

litigation, where many confidential documents were unsealed, many of the risks of these drugs were well-known and documented before they were released to the public without warning. And yet, with the Chantix discovery, 22 million pages of documents and dozens of key depositions are inaccessible and may be forever lost without some sort of intervention. How does this serve public good?

So on behalf of all the silenced victims and unsuspecting Americans, we ask you not to dilute or remove the black boxed warning. In fact, we ask you to strengthen them. These risks have real-life death consequences. Wouldn't you want to know? Thank you.

DR. PARKER: Thank you. Speaker number 7, will you please step up to the podium, introduce yourself, state your name and organization for the record? Thank you.

DR. ZUCKERMAN: Yes, hi. And if you could set my timer on six minutes, I'd be grateful.

I'm Dr. Diana Zuckerman. I am president of the National Center for Health Research. I am the

last speaker, and I hope my voice will hold up. My perspective is on trained and psychiatric epidemiology from Yale Medical School, also a former faculty at Vassar and Yale and a researcher at Harvard.

I've taught research methods courses. I have no conflicts of interest, no financial ties to the pharmaceutical company or to the lawsuits. And the perspective I bring, I will try to tie together all the data that you've been hearing today and make sense of why there are so many conflicting findings.

First of all, of course, I acknowledge that smoking is killing thousands of Americans, and I believe that Chantix should be available as an option for those who can use it safely. But I also believe very strongly that patients and their physicians need a very clear black boxed warning so that they know when to stop taking Chantix if it is necessary to do so.

Mark Twain said, "There are three kinds of lies, lies, damn lies, and statistics." So just to

say, I'm a researcher. I believe in data. But I also have seen it manipulated many times. Let's try to make sense of the different data that we've seen today.

The meta-analysis has various problems that you've already heard about today. Basically, meta-analysis should be based on studies that are similar. And when you have certain studies that, in one case, look at schizophrenics, in another case people who are depressed, those are very important populations to study for Chantix. But they shouldn't be put together in a meta-analysis with patients that specifically have no mental illness.

The observational studies were based on hospital records. You've heard again that that is not the appropriate way to measure these kinds of strange and sometimes difficult to categorize reactions. The adverse reaction reports from physicians are another standard that we've heard today and reports from patients.

As I said, the meta-analysis accuracy

depends on the quality of each study in the analysis and whether they fit together. Data can lie, depending on which studies you include and which ones you exclude from a meta-analysis. And so you shouldn't be mixing different kinds of studies with different kinds of patients.

The psychiatric events, most people with those events are not going to end up in hospitals or the ER. Many are not going to have stories that end up in medical records or at least not reported in ways that are not useful. There are studies showing that many mentally ill people are homeless or in jail. In fact, more mentally ill people are in jail than in psychiatric facilities. And many psychiatric side effects can stop quickly and, therefore, not end up reported thanks to a black boxed warning.

When we look at the studies that showed no impact, they didn't evaluate all the psychiatric side effects. They did not interview patients. They relied on hospital records missing about 82 percent of the adverse events from Chantix. And

they relied on the ER or medical records if they didn't rely on hospital records only.

We know that adverse event reporting is the tip of the iceberg. We know that they have a richness of information that you can't find in very large studies. They are far from perfect. But the sheer volume of the adverse reaction reports that you've heard about today are really very compelling.

If we were to ignore those adverse reports, we'd be basically discrediting thousands of doctors who made those reports. We'd be discrediting thousands of patients who have made those reports directly or to their physicians. And we'd really be telling the FDA to stop their adverse event reporting because what's the point of having it if you're going to ignore it when thousands and thousands of reports are saying the same thing?

So we do need better studies. I'm very glad there will be a study coming out in a year or so. We need studies that follow patients, large numbers of patients for longer periods of time. We need

studies that include patients' reports of their side effects. And that's hard. And I love large data sets, and I love looking at really big studies. But you miss a lot of information when you don't have that sort of richness of patients reporting what happened to them.

Let me just say, I have spoken with some patients who took Chantix. And how would you categorize a man who tells me, "I locked my office at work because I couldn't stand all these uncontrollable thoughts, and I couldn't deal with any other person." How do you categorize that or the person who told me he was in the corner with a blanket over his head, trying to stop feeling what he was feeling? And that was the only way he knew how to deal with it. I don't know how you would categorize that in any large data set.

In conclusion, the Pfizer studies, the studies that they've been relying on, are really fatally flawed, as you've heard, because they are omitting most psychiatric adverse reactions. Deleting the black box would send a message that

thousands of physician's reports don't count, including all these reports of suicides and homicides, but even these other reports that are not as lethal, but hugely disruptive.

Lastly, we strongly urge you to urge the FDA to keep the black boxed warning because it protects patients, and also that the black boxed warning be strengthened by misleading the analysis, the meta-analysis information, from that label because the meta-analysis is greatly flawed. And I'd be glad to answer any questions as would my colleagues. Thanks very much.

DR. PARKER: Thank you. Let me confirm that there's a speaker number 8. I think that's the final one.

The open public hearing portion of the meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of data before the committee as well as public comments.

Now, I would like to go back to

Dr. Racoosin. I will state that we still had a couple of remaining comments from this morning that we didn't address, and I hope that we'll be able to weave those into the upcoming conversation, so I haven't forgotten about you.

Charge to the Committee

DR. RACOOSIN: I want to do some clarification on some questions that came up this morning prior to reviewing the questions for this afternoon's discussion. On Pfizer's slide M-13, they describe some key pharmacovigilance definitions. And their definitions come from the CIOMS working group, which is an international group that works on standardizing pharmacovigilance. But what I'd like to emphasize is that our labeling is guided by the Code of Federal Regulations.

Code of Federal Regulations, Title XXI, Food and Drugs, Section 201.57, describes specific requirements on content and format of labeling for human prescription drugs. And this is what Dr. Brodsky was discussing this morning, but I want

to revisit it for clarity.

So 21 CFR 201.57(c)(1) describes what a boxed warning includes. So "certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box." And just going down further, "The box must briefly explain the risk and refer to more detailed information in the contraindications or warnings and precautions section."

Now, specifically about adverse reactions, again, these are the regulations that guide how we decide what's going into the adverse reactions section. And again, I've highlighted -- and the underline is my emphasis -- for purposes of prescription drug labeling, "an adverse reaction is an undesirable effect reasonably associated with use of a drug that may occur as part of the pharmacologic action of the drug or may be unpredictable in its occurrence."

That section goes on to say that, "You would include those adverse events for which there is

some basis to believe that there's a causal relationship between the drug and the occurrence of the adverse event."

So what I'm trying to emphasize here is that there's some latitude as far as the data or the evidence supporting causality. And I think the message that was conveyed this morning is that we had to be certain about causality to call it an adverse reaction and include it in a boxed warning. But what I'm trying to convey here is that there's not a requirement of absolute certainty about causality, but rather that there's some basis to believe that there's a causal relationship.

So moving on, just to highlight the questions that we'll be discussing this afternoon and that we appreciate your input on, first, discussing how you would weigh the evidence contributed by controlled trial meta-analyses, observational studies, and the spontaneous case reports when evaluating the risk of serious neuropsychiatric adverse events in patients taking varenicline.

The second is the voting question. Based on the data presented on the risk of serious neuropsychiatric adverse events with varenicline, what would you recommend, A, removal of the boxed warning statements regarding risk of serious neuropsychiatric adverse events, B, modification of the language in the boxed warning, or C, retaining the current boxed warning statements and reassessing once the ongoing postmarketing randomized controlled trial designed to capture serious neuropsychiatric adverse events is completed.

Then with your answer to number 2, you'll be asked to explain the rationale for your answer and discuss any additional actions that you think the agency should take regarding the risk of serious neuropsychiatric adverse events with varenicline.

DR. PARKER: Before we go to the questions to the committee in our panel discussions, I'd like to go back and pick up from this morning. We had three members of the advisory, Dr. Pickar, Dr. Morrato, and Dr. Roumie, who were queued up for

clarification questions to the sponsor. And I'd like to go back to them and give them an opportunity to ask those questions for clarification.

I also would like to say that these need to be pointed and answered succinctly and on task so that we can get to the specifics that the FDA really wants us to focus on, but I don't want to overlook specific questions that might provide some clarity to that conversation that are directed to the sponsor.

So Dr. Pickar, let me go with you first and see if you still have a question for clarification for the sponsor.

DR. PICKAR: I think my question was addressed by the FDA, and we snuck it in to the sponsor, and they handled it thoroughly. So I think I'm okay.

DR. PARKER: Perfect. Thank you very much. Dr. Morrato?

DR. MORRATO: And the same for me, the FDA answered my question.

DR. PARKER: Good job. Dr. Roumie?

DR. ROUMIE: I'm good.

DR. PARKER: Now, that was really nice, folks. I mean, come on.

All right. So because I'm a fair person, I know that the sponsor also told me that they had a couple comments that they did not feel like they were able to adequately address. And since they didn't get a chance to try to sneak it in to any answers there, I am going to ask if you have anything very pointed that you would like as a postscript to the presentation so that I don't later get told I didn't do it?

DR. WOHLBERG: Yes. Thank you. I have a couple points to clarify. Dr. Racoosin just noted definitions were drawn from CIOMS. In fact, the definitions of adverse event, suspected adverse reaction, and adverse reaction were taken from the 2010 IND safety final rule.

Also, 201.57(c)(7), the first sentence was not highlighted, which describes the overall adverse reaction profile from all sources in the

safety database. That's what we've been trying to discuss today.

If I could have PM-165, please. Also, while we're bringing up that slide, all of the studies in the 18-study meta-analysis have been published. And to the question of advertising, we still need to contain for a balance in all ads, and DDMAC will be monitoring those ads.

PM-165, this slide shows the case quality overview, back to Dr. Morrato's question and also to the point that was brought up by Dr. Winchell about the value of these reports. We don't discount the value of postmarketing reports, but unfortunately, the majority of these reports don't contain the illustrative narratives that we've been hearing about.

These are all of the Suicide/Self-Injury SMQ postmarketing reports and a breakdown of the information in those reports. The therapy and event dates was only available in 16.2 percent of cases. Medical history, at least some of the medical history, was available in about two-thirds,

concomitant medication only in about half of the cases, event latency in one-sixth of the cases, and information about dechallenge in this particular case, suicide and self-injury, about a quarter for dechallenge and less than 1 percent for rechallenge. And it's important to note that 95 percent of the data in FAERS comes from sponsors.

PM-173. To the comment about all of the cases clustering, these are the times to event or the latency to event, where we have that information in postmarketing cases, again, for Suicide/Self-Injury SMQ. And I don't really see a clustering of time to event for these cases. There is an increase, 27 percent, in patients reporting onset of events 7 days to less than one month after initiation of therapy, but there is also a decision out beyond one year.

PM-162. To your question about rechallenge -- and I didn't provide you with a quantitative answer, so I'd like to do that for you out of respect for the question. The positive rechallenges in the Suicide/Self-Injury SMQ -- we

have 17 positive rechallenges, .2 percent of cases, and 35 negative rechallenges or .4.

Now, when we take those numbers in isolation, it's very difficult to look at absolute numbers when you're talking about postmarketing. We have about 4 million patient-years of exposure with varenicline, and we have about 110,000 cases in the safety database.

So when you look at absolute numbers, it's very difficult to put them into context, but we have these number of cases out of 4 million patient-years of exposure.

PM-42. Dr. Winchell showed us some case examples. I'd like to show you these two case examples very quickly. They're two cases, a 45-year-old white female who developed onset of depression and suicidal thoughts. You can see that both patients had no relevant history. They denied any history of psychiatric adverse events. And in both cases, the events resolved within three days of discontinuation of treatment.

On the left is a case that comes from

postmarketing. On the right is a patient who, on unblinding, was being treated with placebo. This is why we do controlled studies.

S-276, please. Further to that point, patients who are taking placebo do have emergence of neuropsychiatric adverse events, even when they deny a past history of these events. So in patients who were taking placebo on the 18 studies, emergence of sleep disorders occurred in 13.6 percent.

Now, we broke that out into patients who abstain from tobacco based on carbon monoxide and those who continued to smoke. And you can see that in those patients who abstained, what we're probably seeing here is emergence of withdrawal phenomenon. So 21 percent had onset of sleep disorders and disturbances compared to 12 percent, who continued to smoke.

Furthermore, we had onset of anxiety disorders and depressed mood in patients, again, who denied any history of psychiatric disease.

DR. PARKER: And conclusion?

DR. WOHLBERG: The last point I want to make is about 1123. S-286, please. Remember that 1123 is described as an 8,000-patient study. It's 8,000 patients across four treatment groups, so 2,000 additional patients will be treated with varenicline, certainly not a small number. The strength of 1123 is that there is an equal distribution of patients between those who have a psychiatric history and those who don't.

What we've done, because we have 16 studies where we have patients with primarily no psychiatric history versus the two studies in patients who do have a psychiatric history -- remember that the blinded event rate in 1123 is 4.5 percent.

If we model what we see and we distribute the patient incidence rate for the composite endpoint that we're using for 1123, the overall event rate, based on our current data, if we assume an equal randomization between a history of and no history of psychiatric disease, is 4.2 percent. It's very close to what we're seeing in the blinded

therapy.

If you look at patients with and without history, 2.2 percent, without a history, 6.1 percent. The numbers are very close. So while 1123 is certainly going to give us more information, it's additional information. It's not unique information.

Questions to the Committee and Discussion

DR. PARKER: Thank you.

So we'll now proceed to the questions to the committee and panel discussions. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel.

We will begin with the first question from the FDA to the advisory to please discuss how you weigh the evidence contributed by the randomized controlled trial meta-analyses, observational studies, and spontaneous case reports when evaluating the risk of serious neuropsychiatric adverse events in patients taking varenicline.

So if you would, kindly, queue up and let's hear from the advisory as we give our input on the specific questions from the FDA. I see Dr. Roumie has queued up. Others, if you'll note your cards, we'd like to hear from as many as we can. Thank you very much.

Dr. Roumie?

DR. ROUMIE: So I like observational data, but I think, in the end, it becomes the totality of the evidence. Given that I typically trust the totality of the evidence, it seems odd to me that, even in the sponsor's, I believe, appendix 5, their power estimates for the observational studies showed that most of the studies are underpowered to detect serious events.

Also of concern to me, I'm going to echo one of Dr. Gerhard's questions, which was the concern about outcome ascertainment and Dr. West, I believe, really thought, "It's non-differential," but I don't think we've seen anything here that shows that the outcome ascertainment in the observational studies truly is non-differential.

I work at the VA. Most of our estimates of serious mental illness among veterans are closer to 20 percent. So my back-of-the-hand calculation on the number of events that they've captured in the VA study is less than .13 percent among both groups.

So I think there was some significant outcome ascertainment issues in most of these observational studies, which, given the issues with outcome ascertainment and the potential power issue, I'm not sure that we can take our observational studies and say, "Oh. Well, they're no. Therefore, they provide good evidence."

DR. PARKER: Dr. Morrato?

DR. MORRATO: I would agree with everything you just said. And let me just add, since the sponsor was nice enough to provide some additional data, how I am interpreting the case reports. I don't see sufficient evidence to refute the findings of the initial concerns around causality. I found them very severe and disturbing in nature, even if they are a minority of cases. We heard

that both in terms of experts at FDA, who are familiar with looking at cases like these. We heard it from the open public comment.

So I found that disturbing. And while I do appreciate you don't always have dechallenge/rechallenge data on everyone, the fact that there is that data available is supportive evidence. Symptoms go away when patients stop and reappear when they have restarted.

With regard to the consistent time period of action, it appears to be related to the dose titration. The data that the sponsor has provided in PM173 used arbitrary, in my opinion, cutpoints as to doing the histogram. If you look at the FDA's briefing document, the median time to events were clustered around the period of 8 to 14 days for the suicidality analysis and 3 to 7 days for the neuropsychiatric analysis. So in my opinion, that's consistent with a clustering of the time.

Equally troubling is the occurrence, I believe, of the suicidal events in persons without psychiatric history. And I believe, in one of the

FDA's analyses, that rate was up to one-third of the cases being reported.

So in light of that, I didn't find, given what you had just mentioned in terms of the weaknesses of the observational data being poor case ascertainment and reduced sensitivity specificity -- and therefore, the concern is misclassification bias to the null.

Similarly, in the control trials, in which you are not relying on prospectively elicited adverse events and imperfect MedDRA term classifications, I also found the control trial data insufficient to conclude that the product is safe in this regard.

So that's how I was looking at the totality.

DR. PARKER: Dr. Saxon?

DR. SAXON: I'm going to take a somewhat different point of view. While there's a huge emotional appeal to the case reports, I don't find them scientifically very compelling because they are completely uncontrolled. And yes, there are methodologic flaws in some of the more controlled

and rigorous studies that have been presented, but we're still seeing data on thousands of people, both in the real world, in the observational studies, and in blinded controlled trials. And there just doesn't seem to be a signal there.

We can go searching for a signal, but that kind of reminds me of the investigator who comes in with a hypothesis for his study, and the null hypothesis pops up, but the person keeps looking and looking to find a signal that isn't there because the person believes in that signal.

I certainly think that there are rare neuropsychiatric-related events that occur, but I just don't think that they're so common that these case reports would overwhelm the more rigorous data that we have.

DR. PARKER: Dr. Gerhard?

DR. GERHARD: Tobias Gerhard, Rutgers. I find myself somewhat in between the previous comments. So I want to take the current black boxed warning as the starting point, which was put in place based on spontaneous reporting data. We

didn't discuss, I think, these reports in sufficient detail to really have all the information. But they were deemed sufficient in the past by FDA to put the warning in place. I personally may be a bit more hesitant to put in warnings solely based on case reports, but that's kind of where we are, and I don't want to revisit that situation.

So to me, then, the question is whether the new evidence presented today, which comes from meta-analysis of several randomized trials and from several observational studies, is sufficient to alleviate the concerns regarding neuropsychiatric adverse events that are currently in the label in the black boxed warning.

Both the trials and the observational studies share, I think, the major limitation, which is underascertainment of the outcomes of interest. It was nicely illustrated, particularly by the last speaker during the public hearing section. Many of those outcomes would not be necessarily reported in trials that aren't designed to detect them and

certainly wouldn't come to attention and be coded in claims records or medical record systems.

They will therefore affect both the trials and the observational studies. And those measurement issues will very likely result in a bias towards the null. In the context of the question at hand, that means an underestimation of the safety concerns. And this would be the case even if the misclassification is completely non-differential. And that's, I think, the major concern.

The observational studies have two additional problems, and that isn't a statement regarding all observational studies in all contexts, but these specific observational studies. There's the issue of channeling. A patient considered at higher risk might be steered away from varenicline since the warnings were established pretty early after approval.

This also would result in an underestimation of any safety concern or safety risk. And the comparison in some of the studies to bupropion is

problematic because that's an agent that might carry similar risk and is not well-suited to serve as a control to establish evidence for the absence of risk.

All these issues presumably were the reason why FDA in 2009 decided that a dedicated safety trial was necessary rather than an observational safety study, to clarify these questions regarding neuropsychiatric risks.

So I think, taken together, this means that the new data presented today really do not provide information relevant to the question. We really cannot interpret the null findings from the meta-analyses or the observational studies as evidence for the absence of neuropsychiatric risks because they all are subject to significant biases or concerns for significant biases, all of which would be expected to lead to an underestimation of these risks.

So given that a removal of the black box, I think, would likely be interpreted as an assurance of safety, which neither the meta-analyses nor the

observational studies provide at this point, I think it would be a premature step at this point, without having the results of the ongoing safety trial, which is obviously underway and reasonably soon, these results will hopefully be available.

DR. PARKER: So let me remind people, as we discuss to not weigh in on the vote, which is upcoming, but to basically think out loud about how you look at and weigh the evidence to give the FDA insight on how the advisory members are thinking as they approach the evidence. Dr. Grieger?

DR. GRIEGER: It's extremely difficult to prove the negative without some degree of doubt that it may not be negative. And on the other hand, an absence of evidence isn't evidence of absence. So I think we're stuck on that level here. And I think moving away from just the details of the studies themselves, a serious risk doesn't have to be a common risk.

To the extent that there is a serious risk, by whatever measure you want to make that, all the warning does is it advises the patient to be aware

of it, and it advises the doctor to be aware of it, so an increased monitoring and observation can be implemented. It doesn't say don't use the drug. It simply says if you're going to use this drug, be aware that there are reports and there may be a risk. That's really my thought on what a box does.

I'm a psychiatrist, a clinical psychiatrist, so a lot of my drugs have -- all the antidepressants have black boxes as a class boxed warning. Psychiatrists know that, but the problem is most people who prescribe psychiatric drugs aren't psychiatrists. So they didn't learn that in the residency that when you start somebody on an antidepressant medication, who by definition is depressed or has some depressive symptoms, you need to watch out as you re-energize that person, that they may do something that they haven't previously done. It's just a warning. It's an advisement. It's something to take into consideration. Thank you.

DR. PARKER: Thank you. It sounds like you may still have a job. Dr. Marder?

DR. MARDER: I was persuaded by the talks of Dr. Winchell and Dr. Chen that the database, particularly of the observational studies, greatly underestimate a signal, particularly a signal that's vague and hard to describe by individuals. My assumption had been that these more terrifying incidents -- that underneath them, in larger trials, you would see people had -- where their subjective experiences weren't manifest in violent behavior or suicide, but you'd at least see a signal.

But in order to see that, you'd really have to ask the right questions. And they would have to be subtle questions asked in an expert manner, which I believe this next study may do. But right now, I wasn't persuaded that the data that they were actually using was sufficient to dismiss the idea that there was subjective experiences that might have been relatively common, but at a milder level, that would have indicated that there would be stronger signals in certain individuals.

So I think there's just this danger of

underreporting.

DR. PARKER: Dr. Michelson?

DR. MICHELSON: I guess I would just start by stipulating it seems a little bit odd to have this conversation in the context of what seems like pretty soon coming a lot of relevant data. And it just makes it harder to kind of know how to approach the question.

But at least thinking about it a little bit from an industry perspective, I had a couple of thoughts. So the first goes to the comment that you made a few moments ago about the warning. And I think the point there is simply that a black boxed warning is sort of a different level of -- it creates a different level of urgency, immediacy, concern. There are other warnings that are typically in labels, and I don't think the sponsor is proposing that you wouldn't mention these things or raise them as concerns.

The broader thought I had about it really went to Dr. Temple's comment earlier about what does it take to get it out if it oughtn't have been

there, how do you understand that. Is it really, do you use the same level of evidence? Do you kind of go back to the same place? Or is in fact there a higher standard? I mean, intuitively, it seems like it's a lot easier to get something in than it is to get it out.

But having said that, I was struck by the agency's -- in the agency's presentation, you gave a very measured, thoughtful critique of the observational studies, of the clinical studies, and where their deficiencies are, and/or potential deficiencies, why they might potentially not find something.

But as a standard of evidence, I mean, I think you said it well. There's still way beyond the postmarketing surveillance reports, which -- as far as showed, it's just really, really hard to interpret those without understanding background rates and having a denominator, without understanding all the biases that may be driving them.

I would have to think, to your point, that

if we were back in 2007 or 2008, whenever this was, and you had these data, and you were weighing those events against them, it would be awfully hard to give more weight to the postmarketing events in the setting of this overall data.

Having said that, again, I go back to where I started, which is with more data coming, it makes it certainly a more complicated question.

DR. PARKER: Thank you. Dr. Augustson?

DR. AUGUSTSON: Following your instructions a little while ago to do some thinking out loud, I don't know that I have anything unique to offer to this, but I'll go ahead and think out loud for a little bit. So in considering the three classes of data, I think they all serve a very different function. And again, this is not going to be anything novel or new to this group. And they all are valuable.

I think the role of a lot of this adverse event reporting that spontaneously emerges is to identify a signal and to identify the nature of that signal and how it is presented. And then

traditionally, observational studies reinforce the presence of that signal. And then in rare instances, ironically, tobacco use and cancer being one of them, observational studies can lead to a determination of causality, although ultimately we turn to the randomized clinical trial because that gives us the ability to really control for compounds, and then we get to be all science-y at the end of the day.

So if I think about the data that was presented today, I would say that, yes, I think there were some significant methodological flaws, but at the same time, I really do feel like this is a very nice body of research.

However, I also feel like substantial doubt has been raised about whether or not these studies were ascertaining the right outcome. And that to me becomes a huge sticking point in thinking about how to understand all of these wonderful, great studies. But what if they are measuring the wrong thing? Then they're wonderful, great studies that are not really of value in trying to address the

question that we're trying to answer today.

Again, to echo one of the themes that has emerged, we're on the cusp of getting data from a study that, at least from what it sounds, has been specifically designed to answer the potential fundamental flaws of all the other data that we've seen today and we've seen over the last several years.

So it seems, again, very odd to me to be saying, well, let's take it back off because what if we have to put it back on? And to me, there's a very important issue here, which is consumer confidence. And we heard some of this from our citizens who were commenting on this.

If we are in a situation where we have cause for concern, we decide that we send a message, oh, we actually don't have cause for concern, or, well, our concern wasn't as great. That's a black and white statement. Clearly, there would still be substantial warnings within this. And then we put it back on. I think that undermines this agency's ability to maintain confidence in the

eyes of the American public.

I do think, although that's not necessarily a scientific question -- and also remember I work for the National Cancer Institute, so this expresses some bias, although it's not the opinions of the institute --

(Laughter.)

DR. AUGUSTSON: -- I think when we make actions that undermine that confidence, that has a significant impact on our ability to effectively communicate with the American public, and that's not a trivial matter. And I'll stop there. Thank you.

DR. PARKER: Thank you. Mr. Byrd?

MR. BYRD: Without saying a lot of the same things that have already been said, evaluating this data from a patient perspective, from a patient who's taken Chantix, I am glad to know that my experiences with the drug was not unique and that this other data is showing an incidence, some signaling of effects that can become very adverse. And when weighing this data equally in its

totality, if there are any conflicts or questions, from my perspective, I must err on the side of protecting the public health and the patient's best interest.

DR. PARKER: Dr. Emerson?

DR. EMERSON: I'm a fan always of trying to take the totality of the evidence, and while randomized clinical trials are my lifeblood, I recognize there's some questions that just cannot addressed in them due to the scientific setting.

That having been said, the sponsor -- I believe it was Dr. West -- was making comments about the Bayes factor in the study. And I think it was being presented not quite in the correct light there, but it is a very important concept, as the Bayes factor is a very good measure of how much a study should sway you based on what you believed beforehand.

In a very simplistic setting, a Bayes factor is the power divided by the type 1 error. So we can talk about what these studies do and have in terms of power. And that has been spoken to, not a

lot and certainly not a lot addressing exactly the admittedly anecdotal experiences of the patients who put in these case reports. We are trying to get at it in a rigorous manner, but it's not always going to do it. And then even, too, they weren't highly powered even for what they were trying to answer.

Then in terms of the type 1 error, the question is always one of, when did you decide to submit this data? Did you ask the question first and register that this was a really good design, just like we do in a clinical trial, or did we submit it all without really knowing what data was collected, and what was there, and how was it selected? And things like that are very, very important.

So it's been raised, the question about what things went into the meta-analyses, what sort of patients were chosen, why did we choose U.K. instead of Hungary. And admittedly, there's lots of reasons to do that.

I'll also note that in statistics, just as

in medicine, just because somebody thinks something works doesn't mean it all absolutely does. The trouble is that in medicine, we try to push people into doing clinical trials. And I will say that in my life personally, I have succeeded better at that than convincing statisticians to do the same things about their methods.

So propensity scores, a very nice idea, but it really relies on that you are able to capture all of the variables that physicians are using to decide how they treat patients. And I'd say that the overall mortality in this data, as Dr. Jim pointed out, pretty much argues that we don't understand why people were prescribing it to different patient populations.

So the idea of that benefit overall, for taking Chantix automatically turns into, well, would you really like to take Chantix or would you like to be the sort of patient that somebody prescribed Chantix for? I don't know the difference between those two in this case, and I worry that the propensity score wouldn't pick that

up.

Similarly, instrumental variables rely on this concept that some latent variable is independent of everything else we see. And if we don't have a real good idea of what the prognostic variables are and the fact that we know that some variables are highly prognostic, invariably, it's not a very high proportion of the variability that we have in the data, which just leaves a lot of questions.

So we are just down to the burden-of-proof question. And whatever this prior belief was from the case reports, I don't think any of these studies, whether it be the meta-analysis of the RCTs or the observational studies, whether they have shifted away what the prior fears were. It's just not quite enough evidence. And obviously I am factoring in that, a year from now, there is a better clinical trial in the wings that was prospectively planned.

DR. PARKER: Dr. Rimal?

DR. RIMAL: Thank you. I guess I'm looking

at this and sort of thinking out loud, to follow your instructions.

DR. PARKER: It's actually the title of a pretty popular book, I've been told. I didn't write it.

DR. RIMAL: I guess the way I see it is, we've got labels right now. And what we are being asked is to change that in some form. And so I see the onus on the sponsor to convince us that those labels, as they currently exist, need to be changed. So what is the evidence that is being presented to make that case?

When I look at the body of that evidence in its totality, what I see is that, of the clinical trials, you've got a situation where the outcome measure is not sensitive enough. In the observational studies, they are being underreported. But most importantly, we are banking on a null finding that there is no difference between those two groups to make a pretty substantial change in current practice.

So I am just not convinced that that rises

to the level of the burden of proof that's required.

DR. PARKER: Dr. Battisti?

DR. BATTISTI: Thank you. So in looking at the specifics, sort of the hat hinges on if you're going to change a black box to a non-black boxed warning, according to Pfizer, it's based on reasonable possibility, on their M-13 slide. I was disappointed that that's inconsistent with what was presented in the Code of Federal Regulations that we're supposed to look instead at reasonably associated causality. Those are two different meanings, and that should be clear.

So based on that -- I know you don't want our opinion on this, but more or less how we're thinking. So I think it is more of a definition based on current FDA policy of whether something should be in a black box or not. And that's just a yes or no. That's a pretty clear thing, I think.

But if you take a step back, I think it's actually more important that whatever the language is in the label needs to be accurate and correct to

current data. And I'm surprised, actually, where we do think there is a signal, and that is sleep disturbances and disorders, which can be serious and significant, it's nowhere in there, and I'm shocked by that. I was surprised.

Further, I'm equally surprised that the last few sentences in the warning label just to me are not appropriate. They are, at best, misleading and, at worst, promotional, in tone at least. So I think that, even though we may not have the study report that's due in about a year, we could still look at that. I think we do it owe it to the public to be as accurate as possible in whatever language we have today, and I think some of those things could still be addressed. Thank you.

DR. PARKER: Thank you. Dr. Budnitz?

DR. BUDNITZ: I just wanted to add one concept to thinking about how we think about the evidence contributed by the randomized trials and the observational studies. And that is, it was challenging for me to think about the endpoints and if they truly measure the outcome of interest here,

which seems to be a very complicated outcome to try to understand; if it's aggressive tendencies and ideation or suicidal ideation, not looking at the trials necessarily that had specific instruments to try to look at some of these suicidality, but focusing on the trials that did not.

Running a surveillance system that uses MedDRA coding of case reports, I appreciate how challenging it is to try to code and appropriately use that kind of case reporting with MedDRA to try to express the content of the case and also looking at ICD-coded diagnoses for billing or administrative purposes.

Without seeing any validation of how those codes truly represent the concerns of interest, again, kind of harder concepts, even suicide attempts, how well that's reflected in the outcomes of these observational studies, I think it is challenging for me to wrap my head around.

I know that one can raise the point of, well, there may not be differential bias between the two groups, but if something like aggressive

tendencies is essentially zero in one group and somewhat more common in the other, I think there can be differential -- you'll miss something a lot more in one group than the other simply because you're not using the right codes or maybe there are no codes to properly look for.

DR. PARKER: Thank you. Dr. Malarcher?

DR. MALARCHER: So when I look at the evidence from the observational studies -- I think a lot of people have said this already -- I felt that there was incomplete case ascertainment. And that is going to be addressed in the upcoming study through questionnaires, relevant questionnaires.

I also feel like there is bias now in who is receiving varenicline. Specifically, those with no prior history of mental health problems are probably not -- our people with a history of mental health problems are not receiving varenicline, and I think that does put a question on the findings of no effect from the observational studies.

Then regarding the clinical trials, as presented, five of them, as presented, did have a

good case ascertainment, but of those five, the ones that contributed the most cases were the ones in patients with schizophrenia or depression. And so if you just looked at those by themselves, those were pretty much underpowered. And so you can't really make a conclusion about those populations, either, if you wanted to just focus on those groups that contributed most of the cases.

DR. PARKER: Thank you. Dr. Perrone?

DR. PERRONE: Thank you. I think one of the question is that we were trying to look at a lot of data that's been generated in this era in the presence of the black boxed warning. And so we almost need to go into a mode where we didn't have the warning and see what would be happening. And that's one of the things that might happen as a result of us potentially taking away the black boxed warning.

But again, things move very slowly in government agencies and public health. And so we're at risk for doing that without having a real trial of what that would mean. I think everyone

echoed the issues about, in the presence of the black boxed warning, we are getting selection bias in some of the trials.

Not only that, but I think the outcomes that we're looking for are being ameliorated by the presence of people in a trial and in fact having some influence of being monitored so closely for these kinds of effects. There's a lot of biologic plausibility for what might be happening based on other neuroactive drugs. And I think that factors into whether or not we're looking at adverse event reporting as our major issue.

One of the premises of looking at it is whether or not it makes sense. And I think, at least based on other drugs that we might have doubted initially, there is similar neuroactive biologic plausibility.

Then I'm just concerned, obviously -- from my clinical standpoint, I work at an emergency department, and I see lots of patients who are newly diagnosed with cancer, who are lifetime smokers, and who have also just been started on

Chantix by a myriad of clinicians, including otolaryngologists and oncologists at every level of health staff.

I think just having a little bit of a presence of a black boxed warning for all of us keeps kind of our eye on the issue, even when many of these patients have coexisting diseases. So I'm just concerned. That's my out-loud thinking. Thank you.

DR. PARKER: Dr. Pickar?

DR. PICKAR: Yes. Three quick points I'm trying to address as you asked the question. How do you weigh the evidence? The first one in my mind is does the phenomenon really exist? Are there really deleterious or serious adverse behavioral effects of this drug?

As Dr. Grieger said, it could be uncommon. And I'm not talking data now; does that exist as a phenomenon? As someone, both as a clinician and ran clinical psychiatric research, you want to see a phenomenon if it really exists, if you possibly can.

I would take away from today in hearing the observations, so forth and so on, that it does exist, although I'd be very curious if any colleagues on the advisory panel say, "You used to be sharp." But I don't think they do exist. I really don't. I'd be very curious if somebody has that feeling. I'm taking away that they do.

Then the next question is, is it higher than baseline or comparators? And bupropion is an interesting comparator. If anybody has used the drug, there's no question about its potential to cause adverse behavioral effects. The NRT is obviously a little different question. The terrific statistical presentations by the FDA folks, which were so good that I thought I was following them, so it must have been very good

We're hard not to make a -- and I'm trying to be very balanced on both sides. I wish there was going to be a break, and I'd come back and see the data from the RCT, by the way, by the one that's ongoing. I am desperate to see that. But those are very fair points about the comparison.

So one, does the phenomenon exist to my opinion, weighing the data? Is it that it does and is potentially very serious? I do not have a super feel as to how much common it is over the baseline, quite frankly.

The third part, having to do with Dr. Temple's comment, which of course is like the NFL -- and I assume that's where you were talking to -- is that a call on the field, you have the unequivocal evidence in replay to change a call that's already been made. And obviously, that doesn't apply here, but it does at a certain level. I mean, that's just the spirit of the nature of changing something. And that's a fair comment.

So one, to me, this is a real phenomenon, and it affects real people just at a clinical level. B, I do not have a read as to how it compares to the other treatments. To Dr. Perrone's comment about how it just modifies non-psychiatric folks who want to help patients who get this drug, who are not going to be paying attention to that, as a psychiatrist, we see that all the time.

That's a fair point.

So we can't wait to see RCT, and it's going to have to be pretty clear the next time around to move aside something that's already been established.

DR. PARKER: Ms. McCarthy?

MS. MCCARTHY: I wanted to echo Dr. Grieger's comments. As the consumer representative and clinical psychotherapist, I see a lot of people who are on psychoactive drugs. I have a lot of interaction outside of my practice with individuals who are taking psychoactive substances, prescribed.

When I see people -- when people report to me problems that they are experiencing because of the medications that they're on, there is a sense of betrayal that is also expressed in almost a traumatic way because they did not get proper informed consent when they were given the drugs. No one said, "If you stop this benzodiazepine after you take it for two weeks, you could experience serious withdrawal." No one said that to them. No

one even said, "This drug is addictive," even if you don't abuse it.

So I think that it is our responsibility to warn consumers, warn the public about these drugs if there is even a remote possibility of an adverse reaction. Without that, we are taking the decision-making power away from the consumer. Thank you.

DR. PARKER: So I will add just a couple of my own comments on top of the ones I heard, trying to hit on a couple things that I didn't hear as specifically, just to put them on the record. One was that, in the data that were presented, we did hear about a noted prevalence of sleep disturbance. And that's not a part of the black boxed warning, but that came up repeatedly. And I couldn't in my mind ask how sleep disturbances relate to neuropsychiatric symptoms. And in general, we're all supposed to be sleeping better so that we function better. So I wonder about what potential relationship, what that means and whether or not that might not be something that we should also

consider as we're looking. And perhaps that will be considered or captured in the upcoming trial.

That was one area. And then the other one really did relate very strongly to the notion of the consumer voice and hearing it as a public health agency and the notions that came up. I was going to really just underscore the role of trust with the public and the consumer voice.

I don't have the clarity I wish I had about a black boxed warning, and a lot of complicated data, and living in the mesolimbic space, and how we make sure that the health of the public is the primary concern in an area of shared decision making, and of how we really communicate this, and make sure that the public's health is really the primary concern.

So I heard that, but I sort of wanted to underscore because we have two very sophisticated consumers as part of the panel. But I think the consumer voice and how it relates to the consumer deserves underscoring.

So I have the daunting task that I would

happily pass on to any of my dear new friends around the table of trying to summarize what I heard. And so I'll try to do that, but before doing that, let me ask -- maybe I'll say that, and then I'll turn to the FDA and ask you if you are getting what you want from the advisory because I think it's really important to make sure that we are addressing the questions that you've set forth.

Are there specific zones or content that you don't feel like have been addressed that you would like to put back to the committee, or do you feel like we're doing just fine?

DR. RACOOSIN: I think the range of data streams has been covered, but you're still welcome to summarize.

DR. PARKER: No. This is usually where everybody listens because they're just really glad that they aren't having to do this. So this is my attempt. And nothing personal to anyone, but I think it helps record keepers. So these are the notes that I took as we spoke on the question, discussing how we weigh the evidence by the

randomized controlled trial meta-analysis, observational studies, spontaneous case reports when evaluating the risk of serious neuropsychiatric events in patients taking varenicline.

So in general, I'll state a few in-general comments that I heard that I felt like related across those zones, and then I'll note the ones that I heard that relate to any of the specific ones that were listed there. And there were indeed a fair number of comments about black boxed warnings that I have put in a different category.

So in general, in no specific order, some concern about the definition in clarity with the feeling, I believe, that the FDA regulations and what's in the law is what we're going by, but some concern about exactly what the definitions were and where we are with the pharmacovigilant definition versus the FDA regulation.

Doubts about whether or not the correct outcome is actually being captured in the importance of actually knowing that we're measuring

the right thing, and whether or not that's happened in the past, and certainly most importantly whether that will happen with the ongoing trial and the results that are coming forward.

The concern about some arbitrary cut points, pros and cons, the yin and yang of statistics, the limitations, that even with the mesolimbic existence within that, that there's still some things we don't understand.

The notion about -- we had some discussion about propensity scores, about Bayes, how much sway, power divided by type 1 error, where we stand with those; again, highlighting a misclassification as what may be going on and how important it is to get the classification as close to accurate as we possibly can.

Limitations of measurement based on coding; some excitement about being on the cusp of getting good to better data, and the import in general of consumer confidence and not being wishy-washy and in any way, eroding the public trust based on yes, no, yes, in, out, whatever it happens to be.

A notion how difficult it is to prove the negative, and that a serious risk indeed does not have to be common, and how important it is to continue to monitor when there is a concern about a serious risk. It's hard to have conversations when more data are actually forthcoming, again underscoring that people are excited that there is more data currently pending from the field. It should be available in 2015.

A notion that the onus is really on the sponsor to convince us to change the label and some discussion about whether or not indeed doing that does require a bit of a higher standard even though that's not necessarily specifically captured in the regulation, a sense that it feels that way.

Regarding the black box, concern with some of the content perhaps being promotional in tone; a notion that the black box keeps us tuned in, that there's something about a black box that does draw attention that it's a big deal, it's there, it exists. And that's a good thing. But also, they are incredibly common with a lot of medications.

Some specific notions from some committee members that there does continue to feel like there's a signal based on the data that are available and also another comment that there is not complete clarity that there is a signal, without a vote, but more discussed that there appears to be a signal than not a signal, definitely noting that the events are not that common, however, not taking away from the fact that though not common, it does not mean that they are not serious.

Then specific to the various types of data that we looked at, I heard comments about -- and I think some of these really apply across the various types of data. But the comments were often attributed to observational, but I think they relate to the meta-analyses as well in many cases.

Underpowering to detect serious events, outcome measurement again highlighted, concern with channeling, and a higher risk that patients, certain patients, high-risk patients, would be steered away from initiating therapy with the

varenicline, how that impacts and introduces bias; sampling not being representative, and the concern that there could be an underestimate of the signal, based on how we're asking the questions and how we get the data.

One comment that noted the importance of spontaneous case reports in identifying signals and that being their purpose, and the observational studies being what we use to reinforce whether or not the signal is really there, and randomized clinical trials really being used to confirm the existence, and there again being glad that more data is forthcoming.

So I think those are the main comments I have. I hope that I've not missed any major comments by anyone on the committee. I believe we have an FDA comment. Yes. Thank you.

DR. JENKINS: Dr. Parker, in going back to your question earlier about have we heard what we needed to hear, I think it would be useful if you could hear a bit more from the committee about your thoughts about whether the risk that we're seeing

for neuropsychiatric adverse events associated with Chantix meets the criteria for a boxed warning.

I have heard quite a few committee members suggest that they believe that there is an associated risk with these neuropsychiatric events and that they may be serious, but of course it's important to keep in mind that a lot of drugs are associated with neuropsychiatric adverse events, and they may be serious.

So the challenge we always face is deciding which ones are particularly in need of being called out to the prescriber and the patient so that they are aware of that risk, that it warrants a boxed warning. And Dr. Brodsky in one of his slides put out three scenarios where we utilize boxed warnings.

I haven't heard much discussion from the committee about, if you do think there is this associated risk of Chantix for these serious neuropsychiatric adverse events, your thoughts about why that would pull it up to a boxed warning in this case versus other cases, where there might

be serious neuropsychiatric adverse events.

So it kind of is getting to the discussion question that's kind of a preview of your thinking on the voting question, but I haven't heard much discussion about how does it fit into the criteria that we have articulated for when a box is warranted.

DR. PARKER: Maybe we can pull the slide back up that highlights -- I believe there was an FDA slide that specifically addressed the black boxed warning. And I think there's a red circle around that particular criterion that was used at the time that the warning was placed.

Let me ask if we have members of the advisory that want to look. Are you all in line here? That's great. So I need new glasses, and I'm sorry I'm not better. So Dr. Marder, if you would, lead us off. Thank you.

DR. MARDER: Just looking at reason two of the boxed warning section, that if there's a serious AR that could be prevented or reduced in frequency or severity by appropriate use of drug,

and I think here, it fits that category because a clinician making a patient -- and perhaps that patient's family member -- aware of something that's unlikely but could be serious would really decrease the risk of that adverse event.

So I think it fits into that particular category very well, as do other kinds of psychiatric warnings.

DR. PARKER: Dr. Saxon?

DR. SAXON: I want to make a few additional points. First, in regard to whether there would be adequate ascertainment of severe or serious neuropsychiatric adverse events in the clinical trials, as someone who has been engaged in a lot of clinical trials, both on the ground, actually seeing the participants, and collecting adverse event information from them, and as an investigator on multi-site trials, where I am looking at reams of adverse event data that are coming in from the various sites, I think it's possible, even using an open-ended question, that subtle neuropsychiatric events might be missed. But I really find it

unlikely that more serious and more severe events would be missed because I think the participants are very likely to report everything that's going on with them if you do ask them if they've been having any issues or any problems.

Secondly, it's maybe a little off topic, but I want to address the questions about alcohol and varenicline interactions that were raised. And first of all, all of the kinds of neuropsychiatric adverse events that we're talking about could be caused by alcohol ingestion alone. There doesn't necessarily have to be an interaction.

But people should also be aware that the NIAAA conducted a phase 2 randomized blinded controlled trial of varenicline as a treatment for alcohol use disorder and as a phase 2 somewhat small study. But actually, varenicline was, in that small study, efficacious at reducing heavy drinking, and they didn't see any big safety issues. It's about 100 participants, so again, it's not a big study.

Third, going to the point that Dr. Jenkins

made, I think we should think about consistency because there are a lot of medications that don't even have an apparent neuropsychiatric indication. A couple of examples come to mind like propranolol and albuterol, that are very frequently used, that have the same range of neuropsychiatric adverse effects as what we're talking about for varenicline, and they don't have a boxed warning.

So I think we should be consistent and not necessarily stigmatize a medication because it happens to treat a very serious addiction.

DR. PARKER: Dr. Grieger?

DR. GRIEGER: I guess I'd have to put that question sort of back to the FDA because there are a number of instances where black boxes have been applied to classes of medication, where there are not any RCTs. I'm sure -- I mean, maybe there's one, but I have never read an RCT on each particular antidepressant drug that says more people in the treatment phase committed suicide than people in the placebo side of the trial, and similarly, deaths in nursing homes for people

treated with antipsychotics. I don't think anyone prospectively went and looked at those groups.

So I think that I would have to put that back to the FDA. Someone made a determination that no matter what the incidence rate of those events are, it was something that they were concerned enough about to notify families, and providers, and patients.

DR. PARKER: Dr. Gerhard?

DR. GERHARD: Just briefly, in response directly to Dr. Jenkins, from my perspective, the new data just aren't very informative to address the issue beyond what was considered when the black box originally was put in, which were basically the case reports, because, clearly, I would say in the observational studies, the outcomes that were most -- or many of the outcomes that we're concerned with would just not be measured appropriately to make any inferences about either the incidence or the relative risks. And I also have great concerns in clinical trials that were specifically designed to detect those types of

outcomes.

DR. PARKER: Dr. Temple, do you want to make a comment?

DR. TEMPLE: Just about the extension of the warning to members of a class, it's perfectly true, for the antipsychotics studies of a couple of the drugs that were then taken as evidence, that the whole class given to demented elderly was a risk.

For antidepressants, there was a very extensive analysis of all available controlled trials with all antidepressants. And while not every drug showed an increase in suicidality, most of them did. And so it was considered applicable to the entire class. And they all do have a boxed warning for suicidal thinking and behavior in relatively young people. Similar analyses actually showed that suicidality was decreased in older people. But there was a lot of data on many individual drugs in that one.

Can I ask another question?

DR. PARKER: Yes.

DR. TEMPLE: It sounds to me like, at the

heart of what everybody is saying is that they find the case reports very convincing, by which I presume everybody means that this level of distress or hostility, or something like that, even as an isolated case report, is reasonably convincing evidence that the drug did it, which is crucial to the whole thing. That's why the boxed warning was enunciated in the first place. Bbut of course, as everybody knows, those kinds of data don't come with the control groups, so you have to assume what the likelihood is of such serious events in the absence of therapy.

I take it that you -- and we heard this from the public speakers -- think that this level of distress and disorder in someone who never had a problem before really is so convincing that it looks like the drug is likely to have done it. And having said that, people didn't find the additional data convincing that these events couldn't be drug related.

But that first part hasn't been said specifically. I am just curious. I think that my

assumption is that people believe those are individually persuasive even without the control group, because there never is a control group here. I'd be interested in comments on that because that's really at the heart of the box in the first place.

DR. PARKER: So let's turn specifically to that question, and then we can come back to the train that we had going before that. Dr. Erstad, I believe you had --

DR. ERSTAD: Brian Erstad from Arizona. Actually, I'll deal with both of those in one. I think it begins with biologic plausibility. I think that's always a start. Secondly, I think severity comes into it. We've heard that from multiple people. And third, I think the totality of the evidence -- and it really does include isolated case reports because with this kind of uncommon safety data, we're never going to have the kinds of numerators and denominators that really give us confidence to come up with ratus mutsen [ph] [indiscernible].

I guess my next point would be, I really don't think it's all about randomized controlled trials, either. We had a lot of focus, meta-analysis, and the limitations of those. I'm a believer that they're more hypothesis generating than hypothesis resolving. I think we have plenty of examples of large RCTs that ended up overturning the results of meta-analyses.

The observational trials, we heard the limitations of those, but I'm becoming increasingly convinced that the answers to some of these are really going to come through big data. And I think, from an FDA standpoint, we can't do large RCTs on every one of these things that comes up, but as we get larger and larger data sets -- and, frankly, there where actually the myriad of the data, complexity of the data, can actually help us, I think then we can potentially start getting better at picking out some of these signals.

So I am really thinking that, again, we might end up going almost a different route than the classic large RCT and where they are looking at

it from a very big data standpoint to get at these serious but potentially rare adverse effects.

DR. PARKER: I think another comment about the seriousness of the rare adverse concerns with these adverse events is that there's potential harm not just to the person who's taking it, but to another individual or individuals. And so I think that's another factor that enters into how it's weighed and how I think about it when I hear it.

It's kind of like I hear it and I ask myself, can I afford to not believe that in case it's true, even though it may not be coming from a source. Maybe I'd like to see it coming out of a different source, but I've got what I've got, and it is what it is. And can I afford to not take it in and assume that it can be real? Is it worth that risk?

So it is a weighing. So I think the word "weighing" -- and I do think that I weigh it because I don't feel like there's enough in it that I can afford to discount it. So when I hear that, that's how I look at it.

I think the other thing is, when we look at the boxed warning that's on the slide here, I think what's reflected in the actual boxed warning is this contacting a healthcare provider immediately, stopping the drug, it's action oriented. Stop the drug. Contact a healthcare provider with the hope that whatever's going on is stopped because of it. And I think from a public health perspective, I think there's more trust coming from the public when it feels like there's that safeguarding on the behalf of the public that's built into the actual content of the message about what to do.

It's not just, oh, there's some data that says so and so. It's do this. Stop the drug and contact someone immediately. So I think those action points are part of what helps to build within the message itself.

We had some others on the list.

Dr. Michelson?

DR. MICHELSON: Yes. Thanks. So I guess two thoughts. One is to Dr. Temple's question. I mean, it seems to me that, as you get millions of

people exposed to something, I don't find it that strange that some of them will have pretty strong reactions. And again, I'm just not convinced that you can attribute it to drug or that you can dis-attribute it. And here, I'm really speaking more as a psychiatrist and seeing people roll through the emergency room. People do this.

But I guess, just stepping back, I did have one other thought that I think we haven't talked about here, which is we've talked a lot about is there a risk, how much of a risk, what does it rise to, where should it go. The other piece, though, is that I think, I assume, that a boxed warning, as compared to, say, a warning, or a precaution, or nothing, isn't free.

Clearly, the drug has benefits. And it actually has, as I understand it, pretty profound benefits compared to what else is available in terms of helping people to smoke. It works well. So the question would be -- and I don't know the answer. But I guess the question would be how many people are deterred from taking the drug, suffer

the consequences of smoking because they are concerned about a potential behavioral effect that may or may not be true. And obviously, there is disagreement about kind of what the level of evidence for that is. But even if it is true, there still is a risk/benefit question that, I guess, I don't think we've really talked much about.

DR. PARKER: So we have several on the list, and I am going to ask people just to give sort of a quick response to the pointed questions so that we get these back to the FDA before we take a break here. So we've got five more on the list. Dr. Morrato?

DR. MORRATO: I'll make mine quick. I just wanted to underscore the earlier point on consistency. So in my mind, I think Dr. Jenkins's question around does it warrant a boxed warning, for me, the life-threatening potential of the adverse event would put it in that. But on the same token, I think those kinds of events need to be considered or treated equally over time. And I

know this can be challenging as different products get labeled at different points in time.

I don't know enough of the psychiatric labeling to know which ones don't have a boxed warning. I know antidepressants for psychiatric have a boxed warning. I don't know how many are out there that might have a similar kind of adverse event that it hasn't elevated to a boxed warning, but I think that would be important to know.

I believe this came up when you were looking at teratogenic effects around how that was being treated, whether REMS were required or not, depending on that. So if this is occurring enough across drugs, maybe there's some thought as to how to make it consistent.

Why is that important? Well, I think it reiterates back to a few folks, what they've said. It's this sort of confidence in the agency, both in terms of public trust, but also, I think, for manufacturers. It's very, I think, difficult when you have a changing landscape and feeling like you're on an uneven playing field. It just happens

to be when your case came to the agency. So I think it's important every once in a while to look at, historically, where is the labels and being consistent in approach.

DR. PARKER: Dr. Battisti?

DR. BATTISTI: Thank you. Now, I kind of ditto those previous remarks in that -- I mean, obviously, this isn't the only drug that the FDA is struggling with how to determine a causal relationship or not; is it potential or definitely there? Unfortunately, I don't think you're ever going to really know.

My concern is, once the study is available, it may not really give us much more insight. And then what are we left with? And so maybe the emphasis is less on trying to see if there's evidence to support a causal relationship and more about education, about what it really means to have a black boxed warning or not.

Me as a clinician, I am going to give the same response to a patient, if I am considering a drug or not, whether it's a black boxed warning or

a warning. It's still a warning. Now, not all clinicians do that, obviously. You elevate. You're much more careful when it's a black box, but maybe it just needs to be a step back and look at -- it would be helpful for us, I think, to know what types of data you're looking at when it comes to antidepressants and suicide risk because, obviously, they're used for depression, and there is suicide risk there. So there are a lot of confounding variables; when you talk about antipsychotics and risk of dementia in the elderly, a black boxed warning there.

What types of data did you use to make that decision, and what effects does that have? Because this is going to be a question you're going to wrestle with, all kinds of drug and drug classes. And maybe the emphasis, again, is not on whether or not there's a causation, but what do you do when there's a warning? What's the proper way to administer that to a patient and have that discussion?

DR. PARKER: Dr. Rimal?

DR. RIMAL: I think, to Dr. Michelson's point about the efficacy of this drug and getting people off cigarettes to quit smoking using a dangerous drug, I feel like the question we are being asked is not should we pull this drug from the market? The question we are being asked is should we do something with the black box?

The product will still continue to be made available. It's just that we're putting information, more accurate information, out there.

DR. PARKER: Dr. Gerhard?

DR. GERHARD: Just very briefly to Dr. Temple's question, I actually would have significant concerns to just put a black boxed warning into a label based solely on case reports. I think, even if the individual case reports are incredibly compelling, as you said correctly, given that there are no comparisons, we just don't know whether it is due to the drug.

But I think, here, the situation is slightly different because the warning is in the label. So we need to have something to trigger that we take

it out. And I don't think that information is there in studies that basically didn't look at the outcome of interest here. And I see that there's a disconnect, but that's how I feel about it.

DR. PARKER: Dr. Budnitz?

DR. BUDNITZ: To address Dr. Temple's question, I think something that might be compelling about these case reports is that it's a possibility of acute risk, and the benefit is the preventative benefit. So kind of like for vaccines, where there might be a higher duty to inform of a risk or due to mitigate risks, when we have a healthy patient, that might be something that is implicit in our understanding or our perception of these acute risks in the case reports.

DR. PARKER: Dr. Pickar?

DR. PICKAR: The comment I started with was, are these real phenomena? I was curious what people felt, and I'm sort of getting some of that feedback. Dr. Temple may have just been a little Socratic. That's the wrong word. But when you

tell me, I was not viewing these as being hostile. I'm hostile on a bad day.

These are very serious disturbances that are life-threatening to other people in most cases. That's what I was viewing. And if I'm off on that, that's important. I'm not defending what I said, but I'm curious. I wasn't kidding about it. I'm very curious whether other people felt that way. And I heard from Dave Michelson, whom I've only known for 30 or 40 years, really question the seriousness of the behavioral toxicity.

I'm not talking about frequency or comparative. You were really raising the question, does this really happen. Is this attributable to that drug? And it's difficult to answer, but that's what we're being asked. I mean, we're sitting here trying to do something with that.

I came down on the side that I believe that when people get interpersonally hostile or physically involved, I didn't exactly hear psychoses. I just couldn't quite get them. I know them, but I couldn't quite get them from these

observational data.

But the nature of these reports, Lord knows we're living every day with what serious mental illness can do in terms of violence to other people. It's a real thing. So I take it seriously.

On the other hand, a fair thing may be, yeah. You're right, Pick, but this drug doesn't cause that. And that's what I was trying to struggle with. And I came on the side that there are cases that were, to me, believable and it's a real phenomena. Frequency, I don't know. Comparative values, I can't judge from the data

So that's what I was asking. I'll ask Steve Marder or anybody else, who lives in the world where we look at these things all the time, what they think. I'm curious. I really wanted feedback on that.

DR. MARDER: I can just reply to him. I think what was said is it's biologically plausible and expected. And when something occurs in a number of people who have had no previous

psychiatric disorder, all of a sudden -- this is in a new population -- I think you take those two together, it raises alarm. Again, it's hard to prove, but it's persuasive.

DR. PARKER: So we're going to take just a 10-minute break. And we're going to come back, and then we will turn to the voting question. And during the break, get ready. Thank you.

(Whereupon, a brief recess was taken.)

DR. PARKER: Let's get ourselves together here and begin. Let's begin. Thank you. So I think the members of the advisory, and I know the FDA, are well aware that we have one voting question. And what we will start with, I will read the question out loud. We will begin by asking members of the advisory that'll be voting what questions or comments concerning the wording of the question that they had out as a beginning. Let's make sure we understand and get the clarity on what it is we're actually voting on.

So the question that's been put before us is, based on the data presented on the risk of

serious neuropsychiatric adverse events with varenicline, what would you recommend?

A, removal of the boxed warning statements regarding risk of serious neuropsychiatric adverse events; B, modification of the language in the boxed warning; or, C, retain the current boxed warning statements and reassess once the ongoing postmarketing randomized controlled trial designed to capture serious neuropsychiatric events is completed.

So I do have one logistical question because I've got yes, no, and abstain. And my understanding is, we're going to vote for A, B, or C. So I will ask for clarification on exactly what you push for what. It's on the bottom. So if anybody else missed that, this is not a test.

So below this, you will notice, under attend, it says A. And under yes, it says B. Under C, no says C, abstain. There is no D or E, so please don't vote for D or E on this.

So we will be voting for A, B, or C. And what we will do, we're going to clarify the

question first. And then after we clarify the question, we will move to voting. And then we will go around the table and ask that everyone record out loud what you voted on and your rationale so that that gets into the record.

So let's begin with any questions from advisory members about the question itself and clarity on what it means. So if you have a question, please -- yes. It looks like we've got one right there. Thank you, Dr. Augustson.

DR. AUGUSTSON: So I think I understand what FDA means by B. However, the citizens' petitions have raised a very different direction than B might go. And so one way to interpret B would be to lessen the statements that are in the black box, which I think is the intention. However, the consumer feedback we got today was arguing for going the other direction in the black box.

DR. PARKER: So to put that in to question form, does B mean change anything about the language to make it stronger or less strident? What exactly does -- is modification bidirectional?

Thank you.

DR. RACOOSIN: I think it could be either direction, and that is the discussion part of the question, is explaining what you mean by modifying it.

DR. JENKINS: Yes. I would agree. When we wrote this question, we were obviously thinking B might be that you might want to modify to lessen the concerns that are in the warning, but you still want it to be in the box. If on the other hand, you think the box needs to be strengthened, I think you could still vote for B, and in your comments describe that you don't think we should keep it as it is currently. You don't think we should get rid of it. You think we should modify it. And you could say modify in which direction.

DR. PARKER: Dr. Grieger?

DR. GRIEGER: A question. Are we talking about the box that shows up at the very beginning, or are we also talking about the box that shows up at the beginning of the warnings section, or both?

DR. RACOOSIN: It's intended to convey the

same information. The smaller box on the highlights page is a condensed version of the full boxed warning, which precedes the full prescribing information. So whatever comment -- or whichever choice that you make would apply to both of those because the highlights page is drawn from the full prescribing information.

DR. GRIEGER: I bring that question up specifically because the second one is the one that includes weigh the risks and benefits because there is evidence of benefit.

DR. PARKER: Actually, I think the first one also has that. I think both of them actually do. So we do have the documents that were passed around. So just to be clear, what I'm hearing is that this first page, the one that we have that shows the red track-changes, the box has three bulleted points. And on the second page, under the prescribing information warnings -- no, that's not right. Yes, it is. There's a larger box.

DR. GRIEGER: I withdraw my comment.

DR. RACOOSIN: For simplicity, focus on the

full boxed warning on the full prescribe, where it says "full prescribing information."

DR. PARKER: So other questions from the advisory regarding the clarity of the question? Removal, modify, retain as is.

Yes, Dr. Rimal?

DR. RIMAL: Just so that I'm clear, if we vote for B, then we would have a subsequent discussion about what that would entail. Is that right?

DR. PARKER: B would be, in my mind, retain and modify, actually. You don't modify it if it's completely gone.

DR. RIMAL: But how to modify it would be a subsequent discussion topic?

DR. PARKER: Absolutely. And that would be something that you would be asked to put specifically on to the record when the discussion comes about that, yes.

Now, I think, in addition -- so this is clarity on the question. And before we vote, if you have anything that you want to bring out as a

discussion point, we'll give an opportunity for that as well. I'm assuming that that's on your mind right now. So why don't you go ahead? Because clearly, I think I know where you're going with it.

DR. RIMAL: You may or may not. I don't know. But I don't know whether this is within the purview of what we are talking about today, but I'll just put it out there. It comes from one of the citizen comments about interaction with alcohol. And that made me think about interaction with other substances that maybe warrants some -- maybe we should first discuss about.

DR. RACOOSIN: So could I clarify a point? When the labeling was revised in September to add information about the observational studies and meta-analyses, two additional warnings were added to varenicline labeling at that time, one describing the risk of seizures with Chantix, with varenicline, and one describing an alcohol interaction.

So that information, as of last month, is

now in the package insert, in the full prescribing information, and should be in the version that you have, section 5.2 and 5.3.

DR. PARKER: Dr. Pickar?

DR. PICKAR: I just wanted to ask, in number C, does that mean we will reassess, have the opportunity to reassess, or theoretically it will be reassessed? Since we are voting on it, what does that exactly mean, "Retain the current boxed warning and reassess once the ongoing postmarketing is done?"

Just are we voting that we will see this again, or the staff will decide whether there's an advisory panel, you will reassess?

[FDA staff nods affirmatively.]

DR. PICKAR: Right. I just wanted to know what I was voting for. So we won't necessarily get to see that.

DR. TEMPLE: Judy, could I ask you something? If B means modifications either to reduce it or to raise it, doesn't that keep you from getting to the fundamental question in C,

which is don't do anything to reduce it until they see the new data? Maybe making them stronger is a separate question. You don't want a confused answer, and I'm a little bit worried about that because, as written, I thought it was take it away, make it less strict, or don't do anything until you see the new data.

A somewhat different question raised by some is whether you should enhance it, which strikes me as, if that gets to be part of B, I'm worried that you won't hear an answer on whether you should wait for the data before you do anything much.

Think I'm overworried? All right. Fine.

DR. JENKINS: I think, as Dr. Parker said, A is remove it, get rid of it. B is retain but modify in some direction or form. C is retain as is and wait for the additional data to decide where to go then. So it seems pretty straightforward to me that it's remove, retain and modify, or retain as is.

DR. PARKER: I would say that awaiting the data happens no matter what, since we don't have it

yet. And then it will be evaluated once available. So we're not voting on whether or not the study will be completed and the data will be evaluated. That's going to happen no matter what.

So it's remove it, retain and modify it now, or retain it as it is. And all of them will be awaiting the upcoming data.

DR. JENKINS: And another comment to make, the citizen petition that was referenced in the public comments, that was just received very recently. So we have not had a chance to review and evaluate the merits of the arguments made in that petition. And we clearly did not present any of that to the committee today.

So that's late-breaking information that we have not reviewed, and I think the committee has not fairly heard an evaluation of that petition.

DR. PARKER: The only other question I wasn't completely clear on was, with removal, whether or not that can be advertised publicly as removal and the impact that can have on the public's perception.

DR. JENKINS: Yes. Again, what I tried to say is we have very limited experience with removal of boxes. You heard from Dr. Brodsky about removal of the box from Avandia. But there were so many other issues going on with Avandia, I don't think it's a very good model for whether the sponsor then rushed out to advertise that the box had been removed.

There are restrictions on what type of advertising can be done for a product that has a boxed warning. I don't know if we have any experience with a company promoting specifically, we used to have a box; now, we don't have a box.

DR. PARKER: So my recommendation or my discussion point on that would be that it would be good to have clarity on that for this and forthcoming. Yes?

DR. SAXON: I can just make a quick comment on another product that had the boxed warning removed last year, which is extended-release injectable naltrexone, Vivitrol brand name, for liver injury. And very few, even experts, with

that medication are aware that the boxed warning was removed. So at least with that example, it really didn't have an impact yet.

DR. PARKER: I think those are our clarity of question. We will be using the electronic voting system for the meeting. Once we begin to vote, the voting buttons will start flashing, and they will continue to flash even after you've entered your vote.

You'll be asked to press the button firmly that corresponds to your vote, as you recall, A, B, and C on the bottom there. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and vote into the record. We'll ask that everyone also state the

reason why you voted as you did, and we will continue until we have gone around the table here and gotten all the input.

So at this point, I'll ask everyone to vote A, removal of the boxed warning statement regarding risk of serious neuropsychiatric adverse events; B, retain and modify modification of the language based on the language in the boxed warning; or, C, retain the current boxed warning statements and reassess once ongoing postmarketing randomized controlled trial designed to capture serious neuropsychiatric events is completed.

So if everyone will now press the button on the microphone that corresponds to your vote, you'll have 20 seconds to vote. Press the button firmly. After you've made your selection, the light may continue to flash. If you are unsure of your vote or you want to change it, please press the corresponding button again before the vote is closed. Thank you. Let's vote.

(Vote taken.)

DR. PARKER: Everyone has voted, and the

voting is now complete.

MS. BHATT: So the voting results: A is 1, B is 6, C is 11, and no voting is zero.

DR. PARKER: Now that the vote is complete, I'd like for us to go around the table and have everyone who voted state their name, and their vote, and would appreciate it if you would also state the reason why you voted as you did.

We'll see what comments we get from that and if there's further input from the advisory that the FDA still wants at the end of that. So let's begin on this end. Dr. Rimal, if you will, start us off here.

DR. RIMAL: Sure. I voted for B, which was to modify the language. And the reason for that is I think I heard enough compelling evidence to suggest that even some of the more rare events were severe enough that we would need to revisit the language of the box.

DR. ROUMIE: Christianne Roumie. I voted B, which was to change the language of the box. And it was really based primarily on the last line in

the box, which seems more a promotional item about the benefits of quitting smoking. And I didn't think it was appropriate for the black box.

DR. GRIEGER: Tom Grieger. I voted to retain the language as is until the results of the prospective random controlled trial are complete and the analysis is complete. The FDA and the sponsor sat down when this problem was first identified and came up with that plan. The protocol has been approved. Three-fourths or so of the subjects have been recruited. It doesn't make sense to move precipitously until those data are received.

DR. BATTISTI: John Battisti. I voted to modify the language. The last three sentences are inappropriate in a warning. And sleep disorders and disturbances are also neuropsychiatric effects, and there's clear data that those do belong. And I do look forward to the data that's forthcoming, and hopefully that will give us some answers.

DR. PICKAR: I'm David Pickar. I voted for C. I really feel that we need to see the results

of that RCT, which looks well-designed and I think would help clarify to be able to make a more informed decision.

DR. PARKER: Ruth Parker. I voted B for retain and modify, with a suggestion of removal of the last bullet point, which corresponds to the last paragraph, which I think is persuasive and doesn't belong in a black box.

DR. ERSTAD: Brian Erstad. I voted C. There is no compelling case to remove the black boxed warning at this time, given that the primary argument for the black box removal is based on totality of accumulated epidemiological evidence over time rather than any recent large RCT, and the fact that the ongoing RCT may provide more definitive information concerning risk.

An argument could be made for some wordsmithing of the warning, but I'm not sure if such wording changes would alleviate or increase confusion to the end user, especially if the RCT has findings that lead to a subsequent change of labeling just a few months later.

Finally, if and when the wording product labeling is changed, consideration should be given to incorporating the suggestions made by ISMP and supported by some of the other public representatives.

DR. GERHARD: Tobias Gerhard. I voted C. I believe the current data from the observational studies and the meta-analyses are not well-suited to reassure us of an absence of risk, although I have my concerns about the initial black boxed warning that was put in based solely on case reports.

I want to point out that this issue of the data being inappropriate to reassure us of the absence of risk is not the general issue of difficulty of proving a negative. It's not a power issue or related to the width of the confidence intervals. It relates to the point that there are specific concerns regarding some potential biases in both the RCTs and the observational studies, all of which would bias the results towards the null. So it's not this general point of difficulty of

proving a negative.

I voted C, retaining the current wording, but I have no problems with some of the suggestions that were made. I would also say that the safety trial with the outcome assessment, which is I think the biggest issue in the meta-analysis and observational data, where this is hopefully much stronger in the safety trial, might allow us to assess whether the boxed warning is truly warranted or not.

DR. PERRONE: Jeanmarie Perrone. I voted C, to retain the current boxed warning statements and reassess when the future RCT safety data comes out. My biggest concern is that a removal of the black boxed warning would be used as an ex facto endorsement of safety, and that hasn't been demonstrated.

MR. BYRD: Christopher Byrd. I voted B, to retain and modify the language in the boxed warning; first, to strengthen the language, to include sleep disruptions and disorders, and secondly to remove the last line and paragraph of

the boxed warning, as it seems to be promotional in nature.

MS. MCCARTHY: Elizabeth McCarthy. I voted B, to retain and modify, very similar reasons as others have expressed, to remove the last bullet point and to create greater inclusion for other problems like sleep disorders. Thank you.

DR. BUDNITZ: Dan Budnitz. I voted C, to retain and revisit after the postmarketing RCT results. I would add that, if the meta-analysis and the RCT results are included in the additional warnings and precautions, that it would be appropriate for FDA to add their reservations or comment on those studies.

DR. MALARCHER: Ann Malarcher. I voted C. I didn't find the new observational or RCT data compelling enough to remove the box.

DR. MORRATO: Elaine Morrato. And I also voted C. I also didn't see the existing observational clinical data sufficient. And I recommended to retain the current labeling. I agree with many others that the last statement is

odd, not what you normally see. But I do appreciate the spirit, I think, of the information, which is trying to provide a balanced risk/benefit message to offset people becoming overly scared. But I can understand the concerns of others, and so I could go either way on that.

I agree with a colleague that the new data, the benefit of it is really the prospective adverse event ascertainment and solicitation, and it's sufficiently powered. I will caveat it, though, having participated in the rosiglitarone deliberations, both when the warning was first put in as well as when it was removed, just having an RCT trial does not necessarily say you're going to have the sufficient evidence to really make a call.

What was a lot of debate around the table was the quality of that evidence and whether or not the trial was done with quality. And it really wasn't until you had the readjudication that the committee felt comfortable with the data.

So I'm hopeful, as things are moving along with this study, that whoever reviews it will have

good quality data and that the study was conducted as designed.

DR. AUGUSTSON: My name is Erik Augustson. I voted C. I think we saw some very interesting data presented today, and then we also saw some very sophisticated interpretations of that data. And the fact that, for me, we came to the end of the day without a very clear answer indicated that the data did not really add that much more to the current conversation.

I really feel like, with the new data going to be available on the horizon, it makes sense for the FDA to stay where they are right now, and then carefully re-assess the new data to see if that indicates a change.

DR. EMERSON: Scott Emerson. I voted C. I felt that just waiting for the additional data before monkeying with this at all, was what was indicated. And I say that noting that the additional 4,000 patients who will contribute to the Chantix versus placebo is not going to add vast amounts of precision, but according to my back-of-

the-envelope calculations, he'd have about 75 percent power to rule out a risk ratio of about 1.5 if there was truly no difference.

But still, I feel that having that data, particularly broken out by both the psychiatric patients and the non-psychiatric patients, would guide this a whole lot better.

DR. MARDER: I'm Stephen Marder, and I voted C. I considered voting B, but as I thought about the last bullet, I was reluctant to eliminate it because I think that this is a drug that is going to be very useful. It may be underutilized. And I'm concerned that the black box could be suppressing prescribing. And that's a serious concern of mine.

DR. SAXON: Andrew Saxon. There may have been in a time when I felt more lonely, but I can't quite remember it now. So maybe a year from now, I'll either feel foolish or feel like a pioneer. But I go back to what I said a couple hours ago. There may be some serious adverse neuropsychiatric effects of varenicline, but I think, although not

perfect, the more rigorously collected data we do have don't show any signal.

I didn't really have a chance to discuss this, but it goes to the point that Dr. Michelson raised right before our break. As someone who day in and day out is clinically working with patients to help them quit their tobacco use, my experience is that patients are afraid to take this medication because of the boxed warning, and it does deter use.

In the healthcare system I work in, the VA, which a few of us around the table also work in, the VA reacted, as one example to the boxed warning, by putting quite severe limitations on the prescribing. A patient can only get 28 days' worth of medication, and then they can't get a refill. They need to go to their prescriber and get another prescription, and go to the pharmacy and get that refilled, which is a big hassle for the patient and also for the prescriber.

What ends up happening is people try it for four weeks, and they don't finish the course of

treatment. And I think we are talking about -- we're treating a life-threatening disorder that, as was pointed out, more convincingly than what varenicline does, tobacco smoking increases the risk for suicidal behaviors, and I think it also has its own very adverse psychiatric effects.

In the risk/benefit calculus that I'm making, I'm going to lean to treating the patient. And if I am doing a good job as a physician, I am going to monitor the patient. And as we've heard, if people are having some adverse events, they can stop the medication. And all the case reports suggest that for the most part, people get better right away, except for the people who get a bad effect 30 days after they stop taking it, that we've also heard about.

So those are some of the reasons for my decision, and I'm sorry I went on so long.

DR. PARKER: Thank you, and thank everyone for sharing not only your vote, but your reasoning as well. Let me ask the FDA if you feel like you have gotten from the advisory the information that

will help you as you move forward or if there's further input that you'd like, because there's nothing wrong with ending a little early.

DR. RACOOSIN: I think we've gotten what we need.

Adjournment

DR. PARKER: Okay, team. We will now adjourn the meeting. Panel members, please remember to drop off your name badge at the registration table on your way out so that they may be recycled. Thank you very much for your attendance. Wait a minute, one more thing.

DR. RACOOSIN: We want to thank Pfizer for your presentation and bringing this issue up. And we appreciate all the contribution of the advisory committees in helping us think about this challenging question. Thank you.

(Whereupon, at 4:00 p.m., the meeting was adjourned.)